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The Journal of Allergy

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Original Articles

HISTOLOGIC CHANGES IN ALLERGIC AND NONALLERGIC WHEALS*

B. S. KLINE, M.D., M. B. COHEN, M.D., AND J. A. RUDOLPH, M.D.,
CLEVELAND, OHIO

A HISTOLOGIC study was made of 31 specimens of human skin obtained from 27 individuals hypersentitive to ragweed pollen, dust, heat, cold or scratching and from 4 individuals not hypersensitive five, ten, fifteen, twenty, thirty, thirty-five, forty-five, sixty-five minutes, three, six and twenty-two hours after the intracutaneous injection of allergen, histamine, exposure to heat, to cold or to scratching. It was noted that in allergic individuals the injection of allergen rapidly gave rise to an inflammation of the dermis and subcutaneous tissue and that the changes in the first ten minutes and after as early as three hours later were much like those of ordinary inflammation of considerable intensity. Fifteen minutes after injection, however, it was noted in the early inflammatory leucocytosis that 25 per cent of the wandering cells were eosinophilic and that twenty to thirty-five minutes after injection the changes of inflammation not only were pronounced but were most unusual in that the majority of the wandering cells were of eosinophilic type.

In addition, the study has shown that whereas intracutaneous injection of histamine produces but a slight tissue reaction in nonallergic individuals, its effect thirty-five minutes, three, six and twenty-two hours after injection in allergic individuals is almost indistinguishable from that produced by allergen. These findings apparently give some support to the view of Lewis[1] and others that in the allergic individual there is an increased tendency of stimulated or injured cells to release histamine or histamine-like substance which then causes the local reaction. Further study is planned to determine whether or not in allergic individuals the unusual inflammation of one-half hour's duration with marked local eosinophilia may be produced by substances other than allergen and histamine.

When the specific substance is injected into the skin of a characteristically sensitive individual an urticarial wheal rapidly develops which

*From the Laboratory Department, Mt. Sinai Hospital and the Asthma and Hay Fever Clinic of Cleveland, Ohio.

varies in intensity with the degree of sensitivity of the patient. Similarly, when this substance is applied to the nasal or ocular mucous membrane, a rapid vascular or inflammatory reaction occurs associated with the well known symptoms of hay fever. The symptoms in asthma apparently result from a similar reaction.

In clinical practice patients are seen in whom these reactions vary in intensity from very slight to very marked. They are usually reversible and, depending upon their severity, have disappeared in from a few minutes to several hours.

Since the urticarial skin reaction referred to above seems to be the characteristic basic lesion in reversible allergy as seen in man, it was deemed advisable to study the histologic changes produced by allergens at different time intervals and to compare the changes with those produced by histamine, thermal and other irritants.

The study was furthermore undertaken to compare the tissue changes in the skin of allergic individuals injected with allergen with those observed at autopsy in the lungs of asthmatic patients. (Cases recorded in the literature and two cases of bronchial asthma, one rapidly fatal, observed by B. S. Kline, A. M. Young and M. B. Cohen to be reported.)

Patients having hay fever or bronchial asthma due to ragweed pollen or house dust who were demonstrated to be markedly sensitive to the allergen by scratch and intradermal tests and whose blood contained atopic reagins sensitizing the skin of non-sensitive persons by the Prausnitz Küstner technic, were used in this study. (The quantity of this reagin in the patients selected is now being determined.)

An area on the abdominal wall between the umbilicus and the crest of the ilium was shaved. Ragweed pollen extract in 1 : 10,000 dilution and dust extract in 1 : 10 dilution was injected intradermally to produce a wheal 2 mm. in diameter. Histamine solution 1 : 100 was injected similarly in another area at least 7.5 cm. away from the area injected with ragweed. The injected areas were circled with ink so that they could be identified for removal at intervals after the surface phenomenon had disappeared.

Thirty minutes before the time for the removal of the specimen for histologic study a diamond-shaped area containing the two test wheals was blocked off at a distance not less than 5 cm. beyond the areas of reaction using 1 per cent novocaine. At the proper time, wedge-shaped pieces of skin and subcutaneous fat one by three by one cm. were removed from each wheal, care being taken to avoid the areas through which the ragweed extract or histamine had been injected. The tissues were fixed in 10 per cent neutral formalin.

For control purposes, specimens were removed in a similar manner from several individuals who gave hives after exposure to heat, cold or scratching and from non-sensitive persons in whom reactions were produced by histamine alone.

The skin specimens after fixation in neutral 10 per cent formalin were prepared for paraffin imbedding, and cut in the routine manner. In each instance some of the sections were stained with hematoxylin and eosin, others by the van Gieson method and in certain instances some by the Warthin-Starry method. In each case, one or more sections were stained by the Wright method as follows:

Routinely prepared and mounted paraffin sections after removal of paraffin by xylol and xylol by alcohol were rinsed in distilled water; then a mixture of equal parts of Wright's stain and distilled water was poured on the slide and allowed to remain five minutes. The stain was then floated off with slightly acidified distilled water (2 drops of glacial acetic acid to 100 c.c. of distilled water). The sections were then dehydrated with acetone and mounted immediately with Gurr's medium.

The hematoxylin and eosin stained preparations give an excellent general picture of the inflammatory reaction and something of the changes affecting the fixed tissue cells. The Wright stained sections show beautifully the type of the participating wandering cells. It may be of significance that the cytoplasm of smooth muscle cells and the granules of eosinophilic wandering cells take a yellow stain of about equal intensity when prepared by the van Gieson method.

TABLE I

MATERIAL EXAMINED*

12	Skin specimens from individuals hypersensitive to ragweed injected with ragweed extract, removed 5, 10, 15, 20 (2), 30 (4), 35 minutes, 3 hours and 6 hours later.
3	Skin specimens from individuals hypersensitive to dust injected with dust extract, removed 15, 30 minutes and 22 hours later.
2	Skin specimens from individuals hypersensitive to cold† exposed to cold, removed 30 minutes and 3 hours later.
1	Skin specimen from individual hypersensitive to heat‡ exposed to heat, removed 30 minutes later.
1	Skin specimen from individual hypersensitive to scratching exposed to scratching, removed ?
2	Skin specimens from individuals hypersensitive to dust injected with ragweed extract, removed 30 minutes, 22 hours later.
3	Skin specimens from individuals hypersensitive to ragweed injected with histamine, removed 35 minutes, 3 hours and 6 hours later.
3	Skin specimens from individuals hypersensitive to dust injected with histamine, removed 20 (2) minutes and 22 hours later.
4	Skin specimens from individuals not hypersensitive injected with histamine, removed 15, 35, 45 and 65 minutes later.
Total 31	Skin specimens

*Two skin specimens of individuals hypersensitive to cold and to scratching were received from Dr. W. W. Duke of Kansas City to whom we are indebted for the opportunity of studying and reporting the changes in such specimens.
† = (one hypersensitive to certain foods).
‡ = (hypersensitive also to dust and orris root).

At this time, the tissue changes observed will not be given in great detail and only the important findings will be summarized.

HISTOLOGIC OBSERVATIONS OF SKIN SPECIMENS REMOVED FIVE MINUTES TO TWENTY-TWO HOURS AFTER INTRACUTANEOUS INJECTION OF ALLERGEN IN ALLERGIC INDIVIDUALS

Sections made of the skin of an individual hypersensitive to ragweed, removed five minutes after the intracutaneous injection of ragweed pol-

len extract, show slight engorgement of blood vessels and slight edema most discernible in the papillary layer of the dermis. Very few leucocytes are present and these are observed here and there in a few blood vessels in the reticular layer of the dermis. Sections of skin removed ten minutes after injection of allergen show more marked vascular engorgement and edema. There is also an intravascular leucocytosis of slight to moderate degree affecting a few vessels in the dermis. An occasional leucocyte is observed in perivascular location. At this stage, 90 per cent of the leucocytes are of polymorph neutrophile type, the remainder eosinophilic. At fifteen minutes, the picture is that of an early inflammation with moderate congestion and edema, a moderate number of vessels showing few to many wandering cells in the lumen and in the wall. A few leucocytes also are observed here and there in perivascular tissues. At this time, the eosinophiles number 25 per cent of the wandering cells present. At twenty minutes, the picture of inflammation is decidedly more marked, the edema well defined, the vessels in general are engorged and the majority show wandering cells in the lumen, in the wall, and in the neighboring perivascular tissue. Striking and unusual is the fact that eosinophilic cells represent about one-half of the wandering cells. At thirty minutes the changes are somewhat more marked than at twenty minutes, and in one instance the picture is that of a severe inflammation with a marked, almost pure (90 per cent) eosinophilic leucocytosis involving vessels, perivascular areas and tissues of dermis and subcutaneous fat. (In the seven specimens of twenty to thirty-five minute stages observed, the local eosinophilia averages 59 per cent. In two specimens it is 90 per cent, in one 25 per cent, in three 50 per cent and in one 60 per cent.) Except for possibly slight swelling of the muscle cells of small arteries showing a leucocytosis no fixed tissue cell changes are observable in the early lesions. Changes similar to those in ragweed sensitive individuals described above but less pronounced were observed in 2 specimens from dust allergic individuals removed fifteen and thirty minutes after injection of dust extract and in a specimen from a third dust and ragweed sensitive individual thirty minutes after the intracutaneous injection of ragweed pollen extract.

At three hours the local reaction in general is even more marked than at thirty minutes with wandering cells not only in and about the blood vessels but also quite diffusely scattered through the tissues (both dermis and subcutaneous fat). The leucocytosis, however, has altered strikingly. The eosinophiles now represent but 10 per cent of the total. The neutrophiles number 82 per cent and monocytes to the extent of 8 per cent are present in and about the blood vessels, and the picture is much like that of an ordinary inflammation of considerable intensity.

At six hours the inflammatory picture is somewhat more marked than at three hours, with decidedly more numerous (20 per cent) monocytes in the exudate. The neutrophiles number 70 per cent and the eosino-

philes represent but 10 per cent of the total. It is possible that at this stage the inflammation is at its peak.

At twenty-two hours (after the injection of dust extract in a dust hypersensitive individual) the local reaction is still considerable; the cells are present in much the same prcentage as at six hours, and although the monocytes appear fewer in number, many more contain tissue fragments and degenerated cells, especially polymorphs. Furthermore, about 20 per cent of the polymorph neutrophiles in the exudate show various degenerative changes.

The earlier lesions are characterized by a greater engorgement and edema and by the presence of leucocytes within lumina and walls whereas the later reactions show little edema, moderate engorgement and wan-

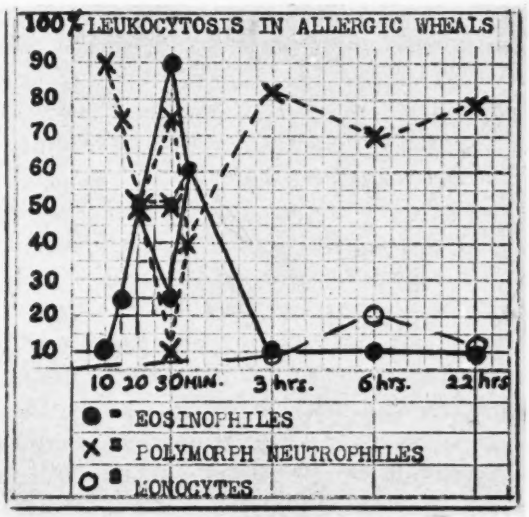

Chart 1.

dering cells especially in the tissues and perivascular areas and fewer in the vessels. The later lesions are also characterized by the presence of a moderate number of monocytes, the twenty-two hour lesion showing many containing cell fragments and degenerating cells. The picture at twenty-two hours is that of a subsiding inflammation, whereas that at six hours suggests an active one possibly at its peak. Both in six hour and in twenty-two hour specimens a few sections show areas of focal necrosis and intense leucocytic infiltration in the dermis and the upper subcutaneous fat apparently representing reactions at the sites of allergen injection. Except for these focal necroses and slight degenerative changes in smooth muscle cells of certain small arteries six hours and more after injection of allergen, the fixed tissue changes are minimal and accord with the clinically observed reversibility of the reactions. At no time are appreciable changes detectable in the epidermis.

Furthermore, although a number of red blood cells and even small hemorrhages are observed at various stages in the reaction, the diapedesis of red blood cells does not appear to be a feature of the process. The pictures rather suggest a specific exudation of leucocytes at first predominatingly of eosinophilic type and later of polymorph neutrophile type. Certainly the most unusual inflammatory picture in the allergic skin was observed in the specimens removed twenty to thirty-five minutes after the intracutaneous injection of the allergen. (See Chart I.)

At the same time that a number of allergic individuals were injected with allergen, a histamine wheal also was produced in a near-by site, and the reactions were allowed to continue equally long. The histologic pictures at thirty-five minutes, three hours, six hours and twenty-two hours in the histamine wheals are almost indistinguishable from those of the comparable allergic wheals. The eosinophilia of the exudate not only is as great in the histamine wheals but is even more persistent than in the allergic wheals. (See Table II).

Careful comparison of the sections, however, shows that the inflammatory reactions to histamine in allergic individuals are somewhat if not decidedly less marked than the reactions to allergen. Of interest is a moderate inflammatory reaction at twenty-two hours following the injection of ragweed pollen extract in a dust sensitive individual also slightly sensitive to ragweed. This reaction while of the same general nature was decidedly less marked than the reaction following injection of dust extract and also definitely less marked than the reaction following the coincident injection of histamine in the same individual.

In contrast to the well defined histologic changes associated with allergic and histamine wheals in allergic individuals are those associated with histamine wheals in nonallergic individuals. Four such reactions observed at fifteen, thirty-five, forty-five and sixty-five minutes show only very slight or slight changes consisting principally of vascular engorgement and of edema with very slight or slight vascular leucocytosis in which polymorph neutrophiles greatly predominate. In the half hour to hour reactions a few leucocytes are present in perivascular location. Similarly in four individuals hypersensitive to heat, cold or scratching exposed respectively to heat, cold and scratching, three specimens removed thirty minutes and one removed three hours later show slight or no detectable changes. (See Table II for summary of histologic observations.)

The histologic changes in the skin of allergic individuals following the injection of allergen, although apparently in great part reversible, and reaching their peak early (at about six hours) bear a certain resemblance to the more severe and longer lasting inflammatory changes in individuals hypersensitive to tuberculin and to those in sensitized or anaphylactized animals following the local injection of specific antigen described in the fundamental studies of Arthus,[2] Arthus and Breton,[3]

TABLE II

Series Spec. No.	Patient	Not Hypersensitive	Individuals Hypersensitive to					Injected With			Exposed to			Skin Specimen Removed										Local Leucocytic Reaction						Cells of Local Leucocytosis (Per Cent)		
			Ragweed	Dust	Heat	Cold	Scratching	Ragweed	Dust	Histamine	Heat	Cold	Scratching	5	10	15	20	30	35	45	65 min.	3 hr.	6 hr.	22 hr.	Date	None	Very slight	Slight	Moderate	Considerable	Marked	Eosinophiles	Polymorph Neutrophiles	Monocytes
1	T. K.			+				+										+							10/ 3/30		+							
2	M. Z.		+					+						+											10/11/31		+							
3	M. Z.		+					+							+										10/11/31			+				10	90	
4	M. Z.		+					+								+									10/11/31			+	+			25	75	
5	M. Z.		+					+									+								10/11/31				+			50	50	
6	M. Z.		+					+										+							10/11/31				+			50	50	
7	S.		+					+										+							9/15/30						+	90	10	
8	A. S.		+					+									+								10/26/30				+			50	50	
9	M. K.		+					+										+							9/25/30			+	+			90	10	
10	M. G.		+					+										+							9/ 5/30			+				25	75	
11	T. B.			+					+									+							10/10/30			+				50	50	
12	W. M.			+					+							+									1/11/32			+					G. P.*	
13	S. A.				+a						+							+							11/ 9/31	+								
14	M. H.					+b						+													10/26/31			+					G. P.*	
15	J. F.					+						+													4/25/32		+							
16	K. D.						+						+												3/12/31	+								
17	S.	+								+						+									1/11/32		+							
18	W. C.	+								+									+						2/11/32		+							
19	G. V.	+								+										+					2/19/32			+					G. P.*	
20	G. P.	+								+											+				2/27/32			+					G. P.*	
21	H. M.			+						+							+								12/29/31			+					G. P.*	
22	W. M			+						+							+								12/29/31			+					G. P. *	
23	A. S.		+					+											+						2/11/32				+			60	40	
24	A. S.		+							+									+						2/11/32				+			60	40	
25	D. S.		+					+														+			3/12/32					+		10	82	8
26	D. S.		+							+												+			3/12/32					+		25	67	8
27	M. C.		+					+															+		4/ 4/32					+	+	10	70	20
28	M. C.		+							+													+		4/ 4/32					+	+	15	65	20
29	L. P.		?	+c					+															+	4/23/32					+		8	79	13
30	L. P.		?	+c						+														+	4/23/32					+		17	75	8
31	L. P.		?	+c				+																+	4/23/32				+			10	80	10

* = Greatly predominate.
a = Hypersensitive also to orris root and dust.
b = Hypersensitive also to certain foods.
c = Hypersensitive also to certain foods and ragweed?

Rössle[4] and Gerlach,[5] especially that of Rössle which includes the changes in early reactions.

The changes summarized above accord in general with those reported by Berger and Lang[6, 7] in a smaller similar series from intracutaneously

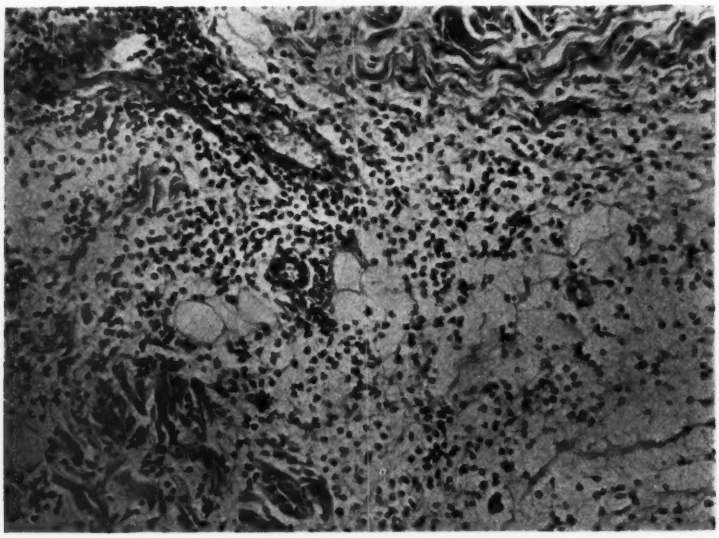

Fig. 1.—Photomicrograph, low power magnification. Skin thirty minutes after injection of ragweed extract in ragweed sensitive patient (marked allergic reaction).

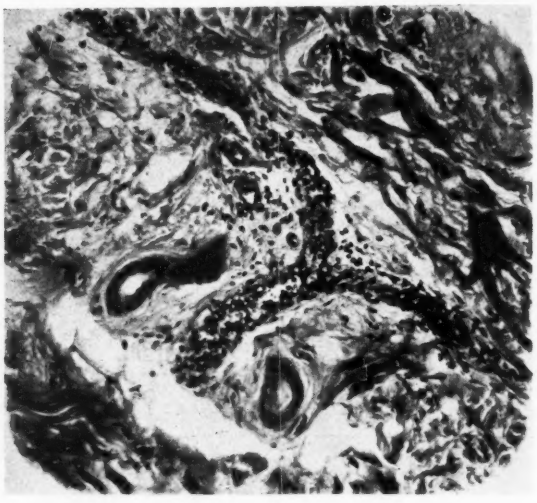

Fig. 2.—Photomicrograph, low power magnification. Skin thirty-five minutes after injection of ragweed extract in ragweed sensitive patient (moderate allergic reaction).

injected allergic and nonallergic individuals, but differ in certain important respects. Furthermore, the present series includes specimens removed from allergic individuals five, ten, fifteen, twenty, thirty and thirty-five minutes and three hours after the injection of allergen not

observed by Berger and Lang. In addition the present series includes specimens from allergic individuals containing comparable coincident allergen and histamine reactions at thirty-five minute, three hour, six hour and twenty-two hour stages.

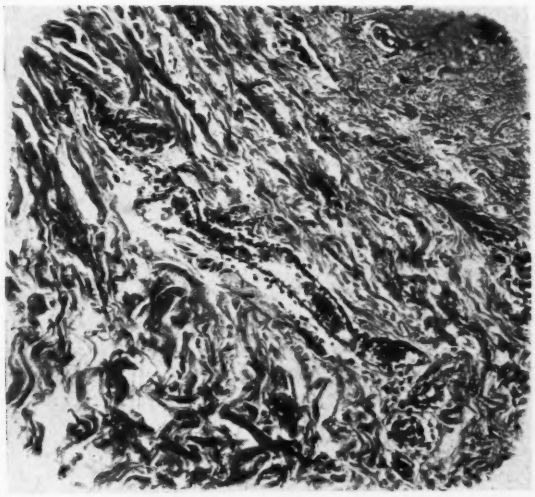

Fig. 3.—Photomicrograph, low power magnification. Skin thirty-five minutes after injection of histamine in nonallergic individual.

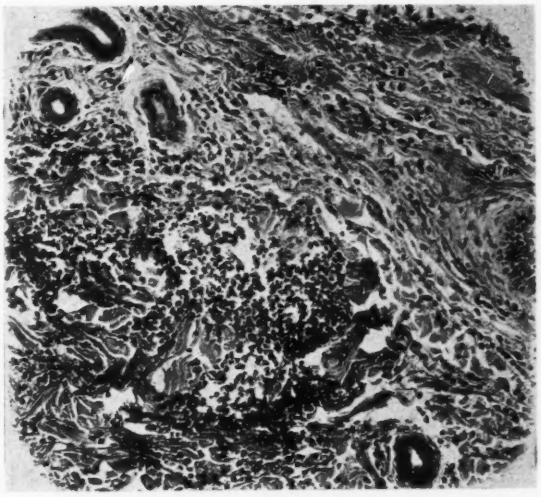

Fig. 4.—Photomicrograph, low power magnification. Skin six hours after injection of ragweed extract in ragweed sensitive patient.

Berger and Lang observed mononuclear cells in the exudate twenty-four hours after but not at seven hours after the injection of allergen into the skin of an allergic individual. In contrast to this, monocytes were observed in our material not only at twenty-two hours but also in reactions of six hours' and three hours' duration.

The principal difference in the two series relates to the number of eosinophiles in the later allergic reactions. Whereas Berger and Lang report a predominance of eosinophilic cells in the exudate at seven hours and even at twenty-four hours, our material shows such predominance

Fig. 5.—Photomicrograph, low power magnification. Skin six hours after injection of histamine in ragweed sensitive patient.

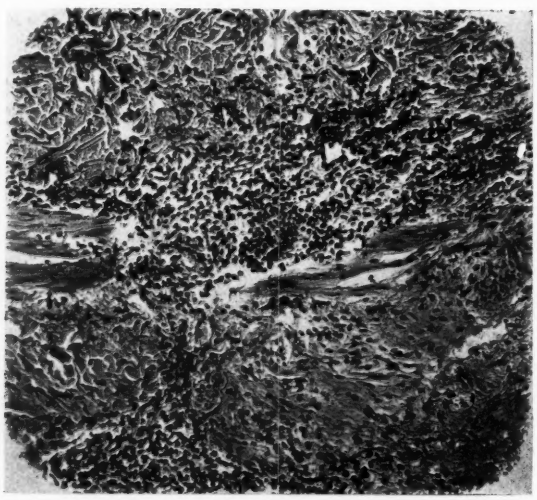

Fig. 6.—Photomicrograph, low power magnification. Skin twenty-two hours after injection of dust extract in dust sensitive patient.

of eosinophiles only twenty to thirty-five minutes after injection of allergen, the picture at twenty-two hours, six hours and even at three hours being much like that of ordinary inflammation of considerable intensity with polymorph neutrophile cells greatly predominating in the exudate. Our results, however, are in accord with the statement of

Berger and Lang that the eosinophilia in the inflammatory exudate while not constant or essential is nevertheless the most characteristic sign of an allergic reaction.

SUMMARY

A histologic study was made of 31 specimens of human skin obtained from 27 individuals hypersensitive to ragweed pollen, dust, heat, cold or scratching and from 4 individuals not hypersensitive five, ten, fifteen, twenty, thirty, thirty-five, forty-five, sixty-five minutes, three, six and twenty-two hours after the intracutaneous injection of allergen, histamine, exposure to heat, to cold or to scratching. It was noted that in allergic individuals the injection of allergen rapidly gave rise to an inflammation of the dermis and subcutaneous tissue and that the changes in the first ten minutes and after as early as three hours later were much like those of ordinary inflammation of considerable intensity. Fifteen minutes after injection, however, it was noted in the early inflammatory leucocytosis that 25 per cent of the wandering cells were eosinophilic and that twenty to thirty-five minutes after injection the changes of inflammation not only were pronounced but were most unusual in that the majority of the wandering cells were of eosinophilic type.

In addition, the study has shown that whereas intracutaneous injection of histamine produces but a slight tissue reaction in nonallergic individuals, its effect thirty-five minutes, three, six and twenty-two hours after injection in allergic individuals is almost indistinguishable from that produced by allergen. These findings apparently give some support to the view of Lewis and others that in the allergic individual there is an increased tendency of stimulated or injured cells to release histamine or histamine-like substance which then causes the local reaction.

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(For discussion, see page 601.)

AN IMPROVED COSEASONAL THERAPY*

WARREN T. VAUGHAN, M.D.
RICHMOND, VA.

IN 1922 I treated a number of patients with pollen allergy who had had no treatment prior to the season but who wished to obtain at least a measure of relief. At that time, the accepted therapy consisted in preseasonal treatment with an abrupt termination at the onset of the season. Emphasis was placed on the risk of reaction if treatment should be given during the season. The cases seen in 1922 were treated very cautiously, with very small doses and surprisingly good results were obtained.[1] The following year Phillips[2] reported satisfactory results from coseasonal intracutaneous desensitization. At the present time coseasonal treatment is quite generally employed, but with the feeling that it is not as satisfactory as preseasonal hyposensitization.

My own experience has been that while the results in 1922 were surprisingly good, they have never been quite so satisfactory in succeeding years. In 1930, for example, satisfactory results were obtained (75 per cent relief or better) from preseasonal treatment in 71.4 per cent, and from coseasonal in but 60 per cent. We had been rather perplexed at this failure to repeat the better results of 1922 until we realized that we were giving larger dosage coseasonally. Our 1922 doses had been timid ones. Those in succeeding years have been bolder. Indeed, we have been attempting to build up the dosage coseasonally very much as is done preseasonally. This, I understand, is the procedure now usually employed by allergists. It is, however, not that which was originally followed in 1922.

In the pollen season 1931 we returned to our original procedure of minute doses, kept small. The results have been as satisfactory as they were in 1922.

The rationale of coseasonal therapy appears to be altogether different from that of preseasonal treatment. In the latter, success depends upon the reaching of a high preseasonal dose just prior to the onset of the pollen season. In Virginia, if the patient is brought up to a top preseasonal dose of 10,000 units (0.5 c.c. of 1:50), or better, 20,000 units, we are sure of adequate relief in 90 per cent of cases. With coseasonal therapy adequate relief is obtained in a large proportion with a top dose of 80 pollen units. It is difficult to imagine that success is achieved with this small dosage by antibody exhaustion or even by the stimulation to production of larger numbers of free antibodies, when one realizes that relief is obtained with 1/250th or even 1/500th of the requisite pre-

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seasonal dose. That there is no antibody exhaustion is indicated by the fact that patients treated coseasonally with minute doses and with relief, still give positive skin reactions and positive ophthalmic reactions and still react positively by passive transfer. This of course is also true although often in less degree with preseasonal therapy. The fact that an individual half desensitized prior to the season will often be worse during the season than the coseasonal individual who has had a very much smaller dosage, indicates that in all probability there is some difference in the mechanism of response.

In 1931 our coseasonal ragweed cases were usually started on a dose of 10 or 20 pollen units (0.05 or 0.1 c.c. of 1:5,000) given daily. If after one or two treatments the patient was not materially relieved, the dose was increased by 20 units each time. As soon as relief was obtained, the interval between injections was increased by one day, then two days, and progressively, as long as relief persisted. With return of symptoms, the frequency of treatment was increased but not the size of dosage. At the onset of treatment the usual precautions were taken to discover unusual sensitiveness requiring a smaller initial dose.

The ragweed season in Richmond in 1931 was heavier than any that has been recorded since we started keeping pollen graphs in 1926. As a rule sufficient pollen is in the air to cause symptoms by August 20 and the peak of prevalence comes about September 15. This is followed by the usual gradual decline. The highest pollen concentration since 1926 had been September 21, 1928, when 189 grains per cubic yard of air were counted. The peak for 1931 was on September 7 with a concentration well over twice this previous peak, 432 per cubic yard. From August 29 to September 14 with the exception of two days the 1931 curve ranged constantly higher than the average for the preceding four years. After September 14 the range paralleled the average for the preceding four years.

In interpreting the results of coseasonal therapy in 1931 therefore we should bear in mind that prior to the middle of September the pollen concentration was much higher than usual and that following the middle of September it was as high as usual. The pollen prevalence first reached zero October 1. There were a few days of low prevalence after October 1.

The following case histories illustrate the type of results obtained.

Mrs. T., ragweed hay fever, started treatment September 1, 1931, with ragweed 20 units (1:5,000, 0.1 c.c.), and adrenalin-ephedrin mixture 0.3 c.c.

September 2	Very much improved.
September 3	Doing nicely, having but little sneezing. Rx. ragweed 20 units.
September 5	Backsliding a bit. Rx. 40 units with adrenalin ephedrin.
September 8	Did splendidly after last treatment but has flared up in the last eighteen hours. Rx. ragweed 80 units.

September 9	A little return of trouble, not much. Rx. ragweed 80 units.
September 13	Doing nicely. Rx. ragweed 80 units.
September 14	Still doing nicely. Rx. ragweed 80 units.
September 15	Doing splendidly. Had some hay fever last night and says this is the only time she has really had any hay fever at all since she started coming. Rx. ragweed 80 units.
September 17	Doing nicely. Rx. ragweed 80 units.
September 19	Not doing so well. Rx. ragweed 80 units.
September 21	Doing satisfactorily. Rx. ragweed 80 units.
September 23	Doing splendidly. No symptoms. Rx. ragweed 100 units.
September 28	Doing nicely. Rx. ragweed 80 units.

From this time on the patient had no symptoms whatsoever, continuing with weekly injections which at the end of the season were gradually increased for perennial therapy.

Mr. B., ragweed hay fever, first dose 20 units, September 4, 1931.

September 5	Possibly a little better. Rx. 60 units.
September 8	No improvement except that he was a little better after the first injection. Rx. 60 units.
September 9	Doing splendidly. Says that the results are excellent so far. Rx. ragweed 80 units.
September 10	Doing fine. Fully 75 per cent relieved so far. Rx. 80 units.
September 11	Doing splendidly. Delighted with results. Rx. 100 units.
September 14	90 per cent relief. Rx. 80 units.
September 16	Relief continued. Rx. 100 units.
September 18	No trouble. Rx. 80 units.

This was followed by injections of 80 to 100 units every second or third day until September 29 when the patient went on weekly therapy with gradually increasing doses for perennial treatment. Five days after the institution of treatment he was 75 per cent improved. Four days later he was 90 per cent improved by his statement, and relief continued throughout the season.

Mr. G., ragweed hay fever, first seen September 8, 1931, at which time he received 20 units of ragweed extract.

September 9	Distinctly better. Rx. 40 units.
September 10	Distinctly better. Rx. 60 units. Omit milk, coffee, banana and asparagus from diet.
September 11	75 per cent relieved. Rx. 80 units.
September 14	Doing nicely. Has had a little flare-up over the week-end. Rx. 80 units.
September 16	Not quite so well. About 50 per cent relief. Rx. 120 units.
September 17	Doing better again. Rx. 120 units.
September 18	Temperature 100.2°. Has a beginning head cold. Rx. rhinopathogen vaccine.
September 19	Temperature normal. Much better. Rx. ragweed 100 units.
September 22	Doing fine. Practically free from symptoms. Rx. ragweed 100 units.

September 24 Patient had considerable headache yesterday and one antrum was opened. No pus, but the headache was at once relieved. Rx. ragweed 120 units.
September 26 Much better. Rx. ragweed 120 units.
September 28 Doing nicely. Rx. ragweed 120 units.
September 30 No symptoms. Rx. ragweed 100 units.

The patient had no return of symptoms and from this last date started on weekly therapy with increasing dosage for perennial treatment.

Mr. Y., first seen August 25 and given ragweed 20 units.
August 26 No change. Rx. ragweed 40 units.
August 27 Doing fairly well although he had some hay fever. Rx. ragweed 80 units.
August 28 Patient had a reaction with urticaria about one hour after receiving his last dose of 80 units. Rx. ragweed 140 units.
August 31 Having considerable hay fever. Rx. ragweed 100 units.
September 1 Doing reasonably well. Rx. ragweed 140 units.
September 2 Doing nicely until about 4 P.M. today when he became suddenly stopped up and has had rather bad hay fever. Rx. ragweed 180 units.
September 4 Still having some sneezing. Rx. ragweed 200 units.

The patient did not return for one month.

October 5 Patient comes in to report he got through the ragweed season beautifully and has had no trouble since the last note of September 4. Note that this intervening period includes the peak of ragweed prevalence for the season.

This case exemplifies the need for small dosage in coseasonal therapy. The addition of a relatively very small dose of pollen extract to the amount already being absorbed through the respiratory tract was sufficient to produce a mild, generalized reaction manifested by urticaria.

Equally good results were obtained with seasonal asthmatics due to ragweed.

Table I, showing results from the three methods of treatment during 1930 and 1931, demonstrates the distinct improvement in coseasonal results for the latter year.

TABLE I

PERCENTAGE OF CASES RECEIVING ADEQUATE RELIEF (75 PER CENT OR BETTER) FROM THREE METHODS OF THERAPY

METHOD	1930	1931
Preseasonal	71.4	84.6
Coseasonal	60.0	86.7
Perennial	100.0	92.5

This principle of small dosage frequently repeated has implications in the treatment of other allergies, particularly perennial inhalant allergy. One may look upon the treatment of sensitization to dust, orris root, tobacco, feathers, etc., as a form of coseasonal therapy in which the season persists throughout the twelve months. Following our good co-

seasonal results last autumn we applied this same principle to desensitization to dust and other inhalants responsible for perennial allergy. In our experience well over 50 per cent of dust sensitive individuals experience distinct relief after the first two or three preliminary desensitizing doses. In such cases there seems little logic in running the dosage on up to a maximum tolerated dose, especially when even at the maximum dose the patient is not completely desensitized but is only hyposensitized. Sufficient hyposensitization to relieve symptoms would appear to be adequate. This dose is then maintained. This also gives a margin for further increase in the event of return of symptoms.

DISCUSSION

In a previous communication[3] on the specific bacterial therapy of chronic arthritis, I called attention to certain apparent differences between bacterial desensitization as applied to arthritis and allergic desensitization in general such as with pollens.

"Successful therapeutic results depend upon the complete avoidance of reactions, either local, focal or general. The occurrence of a focal reaction after vaccine treatment is interpreted as indicating that we are dealing with an organism of etiologic significance but for amelioration of symptoms the dosage must be cut down to where the patient feels better rather than worse after treatment. . . . In mentioning the need for extremely small dosage of pathogen in the treatment of arthritis I would emphasize that . . . when the organism has already invaded the system and the host is already sensitized, minute and carefully graded dosage is requisite."

At that time I felt that there was some subtle difference between bacterial allergic therapy in the common allergies and that in arthritis. If, however, one considers the arthritic as being already in intimate contact with the offending allergen, and views the minute dosage therapy of arthritis as a form of coseasonal treatment, this apparent discrepancy disappears, in part at least.

Our results would indicate the possibility that in those cases in which the individual is already in contact with the offending allergen at the time of institution of treatment, the principle of small dosage frequently repeated applies. The duration of treatment is still uncertain. It has been our experience and that of others that treatment with perennial inhalants must be continued for a long time, possibly indefinitely. With this method as with the larger dosage method the interval between treatments should be spaced as long as possible and should be governed by the symptoms.

The experience herein reported for 1931 is on a relatively small series (15 cases). If the suggestive results can be substantiated by others and in succeeding seasons, it appears entirely possible that coseasonal therapy may become as successful as preseasonal, or indeed may even supplant

it. At the present time the results from perennial therapy remain better than those from either of the other methods, and this appears still to be the method of choice. If, in the end, it is not demonstrated that perennial therapy over a period of years will permanently desensitize, the question will be raised whether the added inconvenience of treatments throughout the year justifies the slightly increased efficacy.

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(For discussion, see page 609.)

PERENNIAL VS. PRESEASONAL TREATMENT OF HAY FEVER*†

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IN 1920 Walker[1] said that "if pollen cases were treated as long and as consistently as animal hair protein cases, many patients would possibly be free from symptoms entirely, for years, if not throughout life." Twelve years have passed since this prediction was printed, and the accumulating evidence indicated that Walker was correct, at least in part.

All of us are thoroughly familiar with the three general methods of specific treatment of hay fever, the preseasonal, the coseasonal, and the perennial. Our percentages of results with the preseasonal method have varied a little in different parts of the country and with the different men who have reported their cases. On the whole, there has not been a great deal of variation in the figures, and all of us have been face to face, many times, with that menace which we call the constitutional reaction.

The battle is on between those who prefer the preseasonal treatment and those who give their injections all year round. It has been argued by those who prefer the perennial method that it is the method of choice because it is more convenient. We must all concede this. The patient's injections are stretched around the year, and intervals exist for out-of-town trips, attention to business, etc. The doctor is greatly benefited because this method scatters his practice and does away with a good deal of the summer "rush."

It seems to me, however, that the choice between the two methods should be not decided by convenience but determined solely by two factors. First, which method gives the better results; and, second, which is less dangerous, or in other words, in which are there fewer constitutional reactions?

SUMMARY OF LITERATURE

Several reports are in the literature. Stewart[2] seems to have published the first article on perennial treatment of hay fever in 1926, but in 1920 Aaron Brown,[3] Vander Veer, Cooke, and Spain,[4] as well as Stewart, began giving injections all year round.

Stewart gives the injections twice weekly up to the end of the hay fever season, then once in two weeks until the following July, then twice weekly again. After two years she gives the treatments every month or two until July, then twice weekly again. Therefore, her method is really

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a combined preseasonal and perennial procedure and hardly answers the question of which is better. She reports excellent results but does not give the percentages of reactions.

Aaron Brown[3, 5, 6] has made considerable contributions. He has pointed out the great advantages of the perennial treatment. He gives the injections once a month, i. e., twelve in all, and demonstrates the greater convenience to the patient and to the doctor. His perennial results are at least 10 per cent better. He avoids reactions by preparing his extracts carefully, by keeping them cold, and each year he changes cautiously from the old to the new extract. No case is worse with perennial treatment. He states that constitutional reactions average about one in every 200 injections but fails to say which method gives fewer reactions.

Vander Veer, Cooke and Spain[4] report excellent results with perennial treatment and seem to prefer the method. However, with their method of giving injections once a month they had five times as many constitutional reactions (0.66 per cent of total injections). The same patients, treated preseasonally the year before, had only 0.13 per cent reactions.

Figley[7] also favors the perennial treatment. At the end of the hay fever season he gives his injections every two weeks, then every three, then every four weeks. The technic is modified in very sensitive cases. His results were good, every case had an equal or better season than with the first year's preseasonal treatments. Six of his 65 cases had no symptoms for at least two years. He also had about one constitutional reaction to each 200 injections, but since he has added ephedrin or adrenalin to his extracts reactions are rare. Figley also failed to compare reactions in the two methods.

Vaughan[8] is highly pleased with the perennial treatment. He gives the injections once in two weeks throughout the year, and only two of his patients had severe reactions. His results in the 1930 season were much better in those treated perennially (100 per cent satisfactory to 71.4 satisfactory in the preseasonal group). He had no severe reactions in the perennial group. Vaughan also points out that this method is especially valuable in the extremely sensitive cases because it gives more time to increase the dosage.

Thommen,[9] collaborating with Coca and Walzer, is one of the few who have tried the perennial method to speak against it. He opposes it because he, along with Vander Veer, had five times as many constitutional reactions with this newer method. It must be remembered, however, that the injections were given once a month.

AUTHOR'S RESULTS

With the two main points, dangers and results, in mind we divided our 1931 cases into two groups. All those included were watched carefully,

took injections regularly and were tested with pollens and other proteins. Those who failed to report regularly were excluded from the series. This left 50 cases treated preseasonally and 38 perennially. All 88 were sensitive to ragweed and 28 patients also had hay fever from grass pollen. Forty-two of the 88, or 47.7 per cent had a history of asthma with the hay fever. Fifty-two per cent of these belonged in the preseasonal group and 42 per cent in the perennial. Positive skin tests to proteins other than pollens were found in 71.5 per cent.

Our method of perennial treatment is similar in many ways to that of Vaughan. The patient is given preseasonal injections about twice a week; we increase the dosage about 50 per cent each time, depending on the patient, of course, until about 0.5 c.c. of 1:100 dilution is reached before the middle of August. Then the amount is reduced to about 0.10 or 0.20 c.c., and the same dose is repeated every two weeks until the following April or May. Then, the dosage is gradually increased without changing the intervals of two weeks; when August comes again, the level is reduced again though usually to a higher amount than previously.

The results are given in Table I and show that a total of 94.8 per cent of cases treated perennially during 1931 were either improved, good, or excellent; correspondingly, the preseasonal group had a total of 76 per cent. Of five patients who had 100 per cent relief four were in the perennial group.

Not only were the results better with perennial treatment, but the difference in constitutional reactions is very striking. There were 34 reactions in the preseasonal group and only 3 in the perennial. The 34 reactions occurred in 18 different patients, one very sensitive man had five moderate spells of hay fever with some asthma. The three reactions in the perennial group were in three different individuals.

TABLE I

COMPARISON OF PERENNIAL AND PRESEASONAL TREATMENT (1931)

	WORSE	SAME	IMPROVED	GOOD	EXCELLENT	CONSTITUTIONAL REACTIONS
Preseasonal (50 cases)	4%	24%	26%	30%	16%	34
Perennial (38 cases)	0%	5.2%	13.1%	50%	31.5%	3
Totals Preseasonal 76% better (1 = 100%) Perennial 94.8% better (4 = 100%)						

COMMENT AND CONCLUSIONS

The weight of evidence is distinctly in favor of the perennial method because it gives better results and is less dangerous. Severe constitutitional reactions are a great hindrance to our work in allergy. To

avoid it some have gone so far as to add adrenalin or ephedrin to their injections and to put on a tourniquet. It is needless to point out that patients object to both of these procedures, the tourniquet is painful, the adrenalin unsettles them. We have shown that constitutional reactions are infrequent if the injections are given once in two weeks, and we are strongly opposed to the opinion of those who give the treatments once a month. The longer the interval the more chance of reactions. Once in two weeks we believe to be the method of choice, and the procedure is not burdensome to most patients.

All this is in addition to what has already been pointed out, namely, that the perennial method is much better because in the very sensitive patient it gives more time to increase the dosage, and because it is more convenient for most patients and for the doctors.

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(For discussion, see page 606.)

DERMATITIS DUE TO CONTACT WITH ORANGE PEEL*

Case Report With Successful Desensitization

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ORANGE has been reported frequently as the cause of allergic eruptions, but instances of specific skin sensitivity to the peel alone are uncommon, Murray,[1] Müller,[2] Fanburg and Kaufman,[3] and Horner[4] reported cases of dermatitis caused by a sensitivity to the peel of orange or lemon. This specific sensitization was confirmed by patch tests (Jadassohn) in three of the patients. The housewife reported by Müller developed a dermatitis of the hands, intermittently, over a period of fifteen years. Eventually, this was noted to occur only after peeling oranges. The observations of Murray and Horner dealt with a dermatitis of the exposed skin of workers engaged in peeling oranges and lemons. The dermatitis seemed to occur most often in "peelers" where there was practically no contact with the juice.

Murray felt that an idiosyncrasy to the bitter orange peel was of etiologic significance in at least one case. Ultimately, this patient developed a persistent dermatitis which required her to discontinue peeling oranges. Horner suggested that limonene, a terpene, which is present in oil of both orange and lemon might well be the cause of the dermatitis. She had the workers in some of the British marmalade factories, oil the exposed skin before peeling oranges and lemons. Following this an injury was rarely sustained. None of these writers reported desensitization with the peel.

Three cases of dermatitis caused by contact with orange have come to our attention. One patient, after preparing an orange daily for a number of years, suddenly developed an erythematous papular eruption on the neck. This reappeared whenever the aromatic spray of oil from the peel came in contact with her face and neck. A patch test of orange peel, applied to the forearm, was negative. The second, a housewife, had a dermatophytosis of the feet and a dermatophytide of the hands. After this had cleared the patient repeatedly developed a vesicular eruption on the hands. This occurred only after peeling oranges and subsided when she avoided this work. The third patient, whose case history follows, developed a severe dermatitis after handling oranges. These patients, as well as those reported by other workers, were able to drink orange juice without ill effects.

It has been shown by various workers that it is practicable to desensitize patients suffering from a dermatitis due to substances with which

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they come in contact. Desensitization to orange peel was attempted in the last mentioned case because of the economic problem which arises from an occupational handicap and the inconvenience of a sensitivity to a common food.

CASE REPORT

M. K., a twenty-seven-year-old fruit and vegetable merchant complained of an intermittent eruption on the hands and arms of one and one-half years' duration. His general condition was excellent and he gave no personal or family history of allergy. For ten years the patient had handled large quantities of fruit and vegetables. He worked about ten hours a day removing wrappers from fruit; trimming, watering, and icing vegetables, and placing small quantities of these foods into bags. In addition, he spent two or three hours a day at the wholesale market sampling oranges. He prepared orange juice almost daily. To amuse his children he had "done tricks" with oranges such as juggling and touching a lighted match to the spray of oil which resulted from squeezing the peel.

The patient's skin had been entirely clear until a few winters previously. Then, especially after handling wet vegetables, his hands became dry and cracked at the finger tips and over the knuckles. About a year and a half previous to admission, when this latter condition was present, the patient noted small water blisters on his hands which itched intensely. His hands then became red and swollen. The local application of ointments and the wearing of gloves while working resulted in improvement. On two occasions when he remained away from work his dermatitis practically cleared. The following winter, while working, the eruption recurred on his hands and began to spread to other areas. He then sought relief.

When first seen the following spring (March, 1931) the patient had an acute pustular and edematous dermatitis which involved the entire hands, a papulovesicular dermatitis with marked edema of the forearms, and a moderate erythematous papular eruption on the chin. The remainder of the skin, including the feet, was entirely clear. Three finger nails were transversely grooved across the outer third and had a serrated grayish border. There was no paronychia. The diagnosis of occupational dermatitis with a secondary pyogenic infection and onychomycosis was made. During this acute stage the patient was treated locally with wet dressings followed by soothing lotions, powders, and pastes. He avoided contact with oranges. It was three months before the dermatitis definitely subsided. Concomitantly, the patient developed a furunculosis which responded to injections of staphylococcus toxin.[5] Recovery was probably delayed by the frequent application of tests, to some of which he showed a marked reaction. During two remissions the patient, against advice, handled a few oranges and within twenty-four hours an acute dermatitis recurred. After the last outbreak had subsided, and the patient was finally convinced that he could not handle oranges, desensitization was started in the hope of making it possible for the patient to resume his occupation.

Cultures.—The affected finger nails and an area of inflamed skin were scraped. A vesicle on the hand was excised. These materials were planted on maltose and blood agar plates. The peel of an orange, to which the patient gave a positive patch test, was also cultured on maltose agar. *Monilia parapsilosis* was isolated from the finger nail, hemolytic *Staphylococcus aureus* from the skin, and a *cryptococcus*, an *aspergillus*, and three mucors were isolated from the orange peel.

Skin Reactions.—It was apparent that the patient's dermatitis resulted from contact with substances met with in his occupation. The possibilities were numerous. He handled a great variety of fruits and vegetables. The patient suspected oranges but thought his difficulty was due to the paraffin spray with which the fruit was treated to prevent the growth of molds. Moreover, the picture of an onychomycosis

was difficult to correlate with the dermatitis unless the patient were sensitized to fungi in his nails or in the fruit. To determine which substances were responsible, the following skin tests were performed:

In March, 1931, patch tests with the tops and leaves of vegetables, and peels and juices of fruits and a commercial preservative used in spraying citrous fruits were applied for twenty-four hours to areas of skin on which the dermatitis had not occurred. All were negative except the area which had been covered with orange peel. Here a patch of vesicular dermatitis developed and persisted about two weeks. Thirty percutaneous tests were made with commercial protein extracts of common foods and contact substances including citrous fruits. All were negative. An intradermal test to orange pulp and juice was negative.

Patch, percutaneous, and intradermal tests were made with extracts of the fungi isolated from the patient's nail and from the orange peel, as well as with protein extracts and carbohydrate fractions of *Monilia albicans, M. psilosis, M. candida,* and *Trichophyton gypseum.* Several positive intradermal reactions were obtained, but as they were not consistent on repetition it seemed unlikely that they were of etiologic significance. A doubtful intradermal reaction was obtained to *cryptococcus* (from the orange peel) and *Monilia parapsilosis* (from the patient's finger nail). All of the patch and percutaneous fungus tests were negative. There was no exacerbation of the dermatitis following the fungus tests.

A month later, when the patient's dermatitis was regressing, the following tests were made on an area of skin on which a dermatitis had not occurred. Four patch tests using the peel of oranges from different localities and one using the undiluted oil of orange peel (*oleum aurantii corticis* U.S.P.) were applied. When these were removed, at the end of twenty-four hours, there was a bulla with a marked inflammatory reaction at the oil of orange test site, and there were irregular red wheals with a surrounding flare at each of the orange peel test sites. The following day the bulla had become pustular, and the sites where the wheals had been were covered with patches of vesicular dermatitis. Even distant areas became involved. There occurred a macular eruption on the face and neck, edema of the eyelids, varying sized wheals on the trunk and legs, and an exacerbation of the dermatitis on the hands and arms. These were accompanied by marked pruritus and general malaise. The reaction was severe enough to require admission to the hospital.

At the time when the above patch tests were applied the patient also received percutaneous and intradermal tests with orange pulp and juice. These were negative. Undiluted oil of orange was found to produce a bulla in normals but caused no reaction when a 1 per cent solution was applied.

Desensitization.—The failure of the skin to react to the pulp or juice of oranges and the marked reactions obtained to the peel seemed to limit the possible cause of the sensitization to some substance in the peel of the orange. Therefore, orange peel was grated, dried, and extracted with ether in a Soxhlet apparatus and the residue extracted with hundredth normal sodium hydroxide. The ether was evaporated and the oily residue mixed with petrolatum. A month later, when the patient's skin was again about clear, he was tested with the above ether and alkaline soluble extracts of orange peel and to 0.1 per cent oil of orange peel. The patch tests to these three substances were positive. The percutaneous tests to the ether and alkaline extracts of the four types of oranges were negative. The intradermal tests to the alkaline extracts of three types of oranges were negative, and the reaction to the fourth (Florida orange) was doubtful. (This was the orange peel from which the cryptococcus had been cultured.)

As the possibility had not been absolutely excluded that sensitization to cryptococcus from the orange peel, or the *Monilia parapsilosis* from the finger nail was a factor in the dermatitis, alkaline extracts of these two fungi were added to the

alkaline extract of orange peel. Subcutaneous injections of the ether and alkaline soluble substances of the orange peel and the alkaline extracts of the fungi were given weekly, beginning with 0.1 c.c. of a 1:10 dilution of the orange peel extracts that would just give positive patch tests and a 1:100 dilution of the fungus extracts giving the doubtful skin reactions. The injections were continued for four months and the amount was increased gradually to 1.0 c.c. of a dilution 1000 times stronger than the concentration of the initial dose.

After the course of injections was completed and when the patient's skin was entirely clear, patch tests with the extracts of orange peel, 1 per cent oil of orange, and percutaneous and intradermal tests with the alkaline extract of orange peel (Florida) were repeated. All were negative.

The patient then began handling oranges in gradually increasing numbers. Within two months after desensitization, he was handling "hundreds of oranges a day" and preparing orange juice. Since then the patient has been observed seven months and there has been no recurrence of his dermatitis. The three finger nails remain serrated and grayish in color at the free border.

Passive Transfer and Agglutination.—Attempts were made to demonstrate antibodies in the patient's skin and blood. The blood serum and serum obtained from his cutaneous vesicles were each injected intracutaneously in two areas of three individuals. No reaction occurred in twenty-four hours. At this time a patch and an intradermal test with orange peel were made on three of these previously injected areas. With one exception, all were negative. In this instance the area which received the patient's vesicle serum and twenty-four hours later an intradermal injection of orange peel extract, developed a regular wheal about 2 cm. in diameter which was surrounded by a moderate erythema. There were no subjective symptoms. This was considered a doubtful reaction.

During one of the patient's exacerbations, some of the vesicular epidermis was removed and extracted with Coca's fluid,[6] tested for sterility and injected intradermally into normal individuals. Patch and intradermal tests with orange peel were made twenty-four hours later. All were negative.

Agglutination tests of the patient's serum with *Monilia parapsilosis* recovered from his finger nail and with *M. albicans* to which his skin reacted were both negative.*

DISCUSSION

The case reported illustrates the course of sensitization and desensitization in a dermatitis of external origin. Oil of orange peel was one and possibly the only effective substance to which the patient was sensitized. When undiluted this oil is an irritant to normal skin. This is true of other substances to which the skin readily becomes sensitized. In concentrations met with in the course of his occupation, orange peel did not at first irritate the patient's skin. He became sensitized only after years of unusual exposure. When once sensitized, any contact with orange peel or the application of a dilute solution of the oil of orange produced a skin reaction.

After protection from accidental exposure to orange, and the injection of increasing doses of extracts of orange peel and fungi, the patient's skin became desensitized. He again handled oranges with impunity. Patch tests to the diluted oil and to the peel became negative. Similar

*These agglutination tests and the identification of the *Moniliae* were made by Dr. R. W. Benham.

desensitization to other contact substances has also been accomplished by oral administration as well as by the external application and the subcutaneous injection of the sensitizing substance. Any one of these methods is apparently effective.

As to the nature of the substance producing the dermatitis, it is clear that the patient was sensitive to orange peel and that the oil of the peel or some substance bound to it was at least in part responsible. Whether proteins in the peel or fungi played a rôle in the sensitization, was not determined.

Most of the evidence points toward an external primary sensitization of the skin and later some degree of capillary sensitization brought out by an intense stimulus. The character of the original eruption and its occurrence on the exposed areas, the positive patch tests, the reactions suggestive of the presence of antibodies in the skin vesicle fluid and of their absence in the blood serum, indicate that the patient's sensitization was primarily limited to the skin (epidermis?). The unusual urticarial response to patch tests which was elicited simultaneously with the burn from the undiluted oil of orange, the doubtful intradermal reaction to the peel extract, and the development of a more generalized urticaria, suggest a later vascular sensitization by the epidermal route. Urticaria also accompanies reactions which seem due to sensitization of the mucosa of various organs. Until our knowledge of these processes is more complete, it is useless to attempt definite conclusions as to the mechanism of many clinical phenomena observed.

SUMMARY

Three cases of acquired sensitization to orange peel are reported.

One was desensitized by subcutaneous injections to an extract of orange peel. Tests that had been positive previously became negative. The patient resumed his occupation and had no recurrence of the dermatitis.

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ALLERGIC MIGRAINE. A REVIEW OF SIXTY CASES*

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IT WOULD seem that proof of the allergic nature of many cases of migraine had been well established by the publication of several series of cases which have been carefully studied. In 1923 Miller and Raulston[1] treated 25 migrainous patients with intravenous peptone and obtained improvement in 84 per cent of the cases. In 1927 Vaughan's[2] report of 10 cases of migraine showing sensitivity to proteins and relieved by elimination of specific foods attracted wide attention. In the same year Ball[3] published a series of 20 cases, in the main confirming the results of Miller and Raulston and showing the allergic inheritance in the families of patients with migraine.

More recently there are the studies of Balyeat and Brittain[4] with 55 cases, of Eyermann[5] with 63 cases, and finally of Balyeat and Rinkel[6] with 202 cases. In Eyermann's series the cases were very thoroughly proved by the elimination of reacting proteins so that the symptoms disappeared and then the production of symptoms by reintroduction of specific proteins.

In spite of this formidable mass of evidence, however, it is apparent that in many quarters the facts are either not known or ignored. In a lecture on migraine before the New York Academy of Medicine in 1929 Frederick Tilney[7] made no mention of the allergic conception of the disease nor did he mention the specific treatment. Barborka[8] in 1930 published a series of 50 cases treated at the Mayo Clinic by ketogenic diets with no consideration of the possibility of allergic reactions. Moehlig[9] in 1931 wrote of a study of 100 cases which were treated with thyroidectomy and thyroid feeding as prominent features. There was no attempt to determine allergic reactions.

In consideration of the above it is felt that there is still need for further publication to throw light on the allergic nature of migraine. Rackemann[10] points out that there is still a need for the study of family histories of migraine patients. Many of the series reported so far contain a lack of specific information about individual cases.

PROCEDURE

The sixty cases serving as a basis for this study I saw in the years 1931 and 1932. They were selected for this series with respect to two criteria, first, a clinical history which would satisfy a good clinician of the diagnosis of migraine; second, a complete routine study.

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The study of the patients included in every case a careful history, a complete physical examination and any special examinations to rule out sinus infections, eye-strain, brain tumor, and gastrointestinal disease. Every patient received the same routine protein sensitivity tests. He was tested to 30 pollens by the scratch method and to 100 foods, epidermals, and miscellaneous substances by the intradermal method. The intradermal tests were performed on the back of the patient by the injection of 0.05 c.c. of a 1:1000 dilution of protein extract in Coca's solution. The tests were read at the end of one-half hour and from eighteen to twenty-four hours later. The extracts were frequently checked for contamination, and those which seemed to be giving a high percentage of positive reactions were frequently replaced. It has been possible in our experience to perform all of these tests on a patient in a half day with no considerable inconvenience to the patient. There were no untoward reactions in this series.

The patients in all instances were instructed to eliminate only the foods to which they reacted. Other reacting substances were ignored therapeutically. No drugs were advised. In many cases because of the large number of foods to be eliminated the Department of Diet Therapy assisted in devising a balanced diet and in instructing the patient therein. In a few cases where too many foods gave positive skin tests the elimination diets of Rowe[11] were used. In some cases where the attacks of migraine occurred at considerable intervals the plan of using food diaries as suggested by Vaughan[12] was utilized.

When a patient reported relief from an elimination régime, he was then instructed to reintroduce into his diet all of the reacting foods singly in an endeavor to ascertain which of the foods actually caused symptoms.

In many cases the information on the results of treatment could not be satisfactorily obtained. This was due to the fact that the great majority of patients seen in the University Hospital live outside of Ann Arbor. Some come as far as 500 miles. For that reason many patients pay one visit to the hospital, obtain a diagnosis, and are referred to family physicians for further management. Thus a large number of patients never return so that the results of treatment can be ascertained by interviews or by questionnaires, and there are certain obvious disadvantages to the use of questionnaires. In the cases where results of treatment have been reported, the data have been obtained by interviews or by questionnaires. In the case of ambiguous answers to questionnaires no result was recorded.

The table sets forth some of the salient points of the series. All patients gave some positive skin reactions. In no case was there lack of evidence of multiple sensitivity to foods. Some of the epidermals usually reacted also, but no definite significance could be attached to these. The

only reactions to pollens were obtained in patients who also had hay fever.

SUMMARY OF CASES

Sex Incidence.—There were 18 males (30 per cent) and 42 females (70 per cent) in this series. (There were 41.8 per cent males and 58.2 per cent females in the series of Balyeat and Brittain.[4]

Age at Onset of Symptoms.—Fifteen cases could not give a definite age of onset but said "in childhood." Of the remaining 45 cases the average age of onset was 21.6 years. The youngest recorded age of onset was four years. The oldest was fifty years.

Symptoms of Migraine and Other Allergic Manifestations.—In making the diagnosis of migraine many difficulties naturally arose. Our criterion was that of severe, paroxysmal headaches associated with various aura and accompanied by nausea, vomiting, visual disturbances, and prostration. It was found that the location of the headaches was not a constant feature. Pure hemicrania was encountered in only a few cases. From the subjective nature of the disease the diagnosis was always considered more probable when a history of accompanying nausea and vomiting could be obtained. This accounts for the fact that in only 14 cases did we make the diagnosis of migraine without the gastrointestinal upsets. In only 7 cases (11 per cent) were visual symptoms encountered which were related to the attacks. Bulimia was a common prodromal symptom. Many patients could predict their attacks by indefinite symptoms and "feelings" which they could not well describe. Parasthesias and paralyses were very uncommon in our experience—contrary to the experience of Balyeat and Rinkel.[6]

There were 11 patients (18 per cent) who had other allergic symptoms. Four of these had hay fever, six had urticaria, three had eczema, and one had mucous colitis.

Familial History of Migraine and Other Allergic Manifestations.—Forty-three cases (71 per cent) gave a history of migraine in blood relations; of these 7 (11 per cent) had migraine on both sides of the family.

Other allergic manifestations than migraine occurred in the families of 31 cases (51 per cent). Only one of these cases had other allergic manifestations on both sides of the family.

If migraine is assumed to be an allergic phenomenon, then the total number of cases giving allergic family histories was 51 (85 per cent). This is in accord with Balyeat and Rinkel who reported 82.1 per cent.[6]

Relief of Symptoms by Elimination of Specific Foods.—Data are available on 42 cases. Of these, 14 cases (33 per cent) had complete relief, 19 (45 per cent) had partial relief, and in 9 cases (21 per cent) there was no relief. So that of the 42 cases, 33, or 78 per cent, showed some results from treatment. This record could probably be improved if the clinic were so situated as to facilitate more frequent interviews with

TABLE I

CASE NUMBER	SEX	AGE	SYMPTOMS					FAMILY HISTORY		RELIEF	MONTHS OBSERVED	REMARKS
			AGE AT ONSET	HEADACHE	G. I. SYMPTOMS	OPHTH. SYMPT.	OTHER ALLERGIC MANIFESTATIONS	MIGRAINE	OTHER ALLERGIC MANIFESTATIONS			
1	♀	25	11	++	++	+++	—	Mother, mat. gr. mother	Mother, asthma; brother, eczema	Complete	3	Mitral stenosis, cardiac failure
2	♂	38	32	+++	+++	—	—	—	Mother, asthma; sister, asthma; sister, urticaria	Complete	1	
3	♂	40	38	+++	++	—	—	Mother	—	Partial	10	
4	♀	32	26	+++	+	—	—	Mother	Mother, asthma, hay fever; daughter, urticaria			
5	♂	71	33	+++	+	—	Hay fever	—	—	None	1	
6	♂	48	18	++	++	—	—	Mother, father	—			
7	♀	46	27	+++	++	—	—	—	—	Partial	1	
8	♀	31	15	++	+	—	—	Sister, sister	—			
9	♀	44	Child.	+++	+	—	—	Father, son	Son, hay fever	Complete	8	
10	♀	37	32	+++	++	—	—	Mother, sister, daughter	Father, asthma			
11	♀	41	26	+++	++	—	—	Sister	—	Complete	9	
12	♂	31	Child.	++	++	—	—	—	—	Partial	4	
13	♀	25	20	+++	+	—	—	—	—			
14	♀	26	16	+++	—	—	—	Father	Pat. gr. father, eczema	Complete	1	Dental extraction aided

TABLE I (Cont'd)

CASE NUMBER	SEX	AGE	SYMPTOMS					FAMILY HISTORY		RELIEF	MONTHS OBSERVED	REMARKS
			AGE AT ONSET	HEADACHE	G. I. SYMPTOMS	OPHTH. SYMPT.	OTHER ALLERGIC MANIFESTATIONS	MIGRAINE	OTHER ALLERGIC MANIFESTATIONS			
15	♀	26	Child.	+++	—	—	Urticaria	—	Pat. gr. mother, hay fever, asthma	None	4	
16	♀	38	4	+++	+++	—	—	Father	Mother, hay fever, asthma	Partial	16	
17	♀	26	Child.	+++	+++	—	Urticaria	Mother, sister, brother	Mat. cousin, asthma	Complete	2	
18	♀	22	18	+++	—	—	—	—	—			
19	♂	22	12	+++	+++	++	—	Mother	Mat. gr. father, hay fever	Complete	16	
20	♀	32	10	+++	++	—	—	Father, pat. gr. father	—			
21	♀	38	21	+++	+++	—	—	Sister	—	None	16	Marked psychoneurosis
22	♀	44	36	+++	++	—	Mucous colitis, urticaria	Mother, father, brother, 2 sisters, mat. aunt, pat. gr. father	Pat. cousin, hay fever; pat. cousin, urticaria	None	12	
23	♂	50	Child.	++++	++	—	—	Pat. gr. mother, father, son	Brother, asthma, hay fever	None	12	
24	♂	42	8	++++	++	—	—	Father, pat. gr. father	Sister, hay fever			
25	♂	25	19	+++	++	—	—	Mother	—	Partial	3	
26	♂	49	30	+++	+	—	—	Mother, sister	—	None	1	

TABLE I (Cont'd)

CASE NUMBER	SEX	AGE	SYMPTOMS					FAMILY HISTORY		RELIEF	MONTHS OBSERVED	REMARKS
			AGE AT ONSET	HEADACHE	G. I. SYMPTOMS	OPHTH. SYMPT.	OTHER ALLERGIC MANIFESTATIONS	MIGRAINE	OTHER ALLERGIC MANIFESTATIONS			
27	♂	21	14	+++	+++	+++	—	Mat. gr. mother, mat. uncle	—	Partial	12	
28	♀	54	18	+++	++	—	—	Mother, father, pat. gr. mother	Mother, eczema	Partial	3	
29	♀	38	12	+++	++	—	—	Mother, sister	—			
30	♀	54	34	+++	++	—	—	—	Father, asthma; sister, asthma			
31	♀	42	30	++++	++	—	—	—	Daughter, urticaria	Complete	10	
32	♀	53	Child.	++	++	—	Eczema	Mother, 2 brothers	Mat. niece, urticaria	Partial	2	
33	♀	26	21	+++	—	—	—	Father	—	Partial	2	
34	♀	55	Child.	+++	++	—	Eczema	Mother, father, sister	Sister, hay fever	Complete	13	
35	♀	25	10	+++	—	—	—	Mat. grandmother	—	Complete	1	
36	♀	51	50	+++	++	—	Hay fever	—	—	Partial	3	
37	♀	33	23	+++	++	—	—	Mother	—	Partial	2	
38	♀	36	15	+++	+	—	—	Father, brother	—	Partial	2	
39	♀	26	24	++	—	—	Hay fever, eczema	—	Father, eczema; mother, asthma; sister, urticaria			

TABLE I (Cont'd)

CASE NUMBER	SEX	AGE	SYMPTOMS					FAMILY HISTORY		RELIEF	MONTHS OBSERVED	REMARKS
			AGE AT ONSET	HEADACHE	G. I. SYMPTOMS	OPHTH. SYMPT.	OTHER ALLERGIC MANIFESTATIONS	MIGRAINE	OTHER ALLERGIC MANIFESTATIONS			
40	♂	83	32	+++	+	—	—	—	—			
41	♂	29	18	+++	+++	—	—	Mother	Sister, hay fever	Partial	3	
42	♂	37	17	+++	—	—	—	Sister	—	Partial	11	Also duodenal ulcer
43	♀	25	17	++	+++	—	—	Mother, 2 brothers	—	None	5	
44	♀	21	Child.	+++	—	—	—	Mother, mat. gr. mother, mat. great gr. mother	Brother, eczema	None	13	
45	♀	28	Child.	+++	—	—	—	Mother, brother	Father, urticaria	Partial	8	
46	♂	36	30	+++	—	—	—	—	—			
47	♀	23	Child.	+++	—	—	—	Mother, father, brother, sister	—			
48	♀	30	Child.	++++	++++	—	—	Father	Sister, urticaria	Complete	12	
49	♂	35	23	+++	—	—	—	—	—	Partial	7	
50	♀	50	Child.	+++	++	—	—	Pat. gr. mother	Sister and brother, hay fever; sister, urticaria	Partial	6	
51	♀	45	Child.	+++	+++	+++	—	Mother, father, daughter	Mat. gr. father			

TABLE I (Cont'd)

CASE NUMBER	SEX	AGE	SYMPTOMS					FAMILY HISTORY		RELIEF	MONTHS OBSERVED	REMARKS
			AGE AT ONSET	HEADACHE	G. I. SYMPTOMS	OPHTH. SYMPT.	OTHER ALLERGIC MANIFESTATIONS	MIGRAINE	OTHER ALLERGIC MANIFESTATIONS			
52	♀	40	22	+++	+++	++	—	—	Mat. gr. mother, asthma; mat. cousin, asthma			
53	♀	29	6	+++	—	—	Urticaria, hay fever	—	Sister, urticaria	Complete	13	
54	♂	30	28	+++	++	—	—	Mother	—			Marked psychoneurosis
55	♀	46	Child.	+++	—	—	—	Father, pat. gr. father, sister, son	Son, asthma	None	4	
56	♀	25	24	+++	++	—	Urticaria	—	Father, pat. uncle, sister, asthma	Partial	5	
57	♂	52	10	+++	+++	++	Urticaria	Mother, father, sister	Sister, asthma	Partial	4	
58	♀	28	18	+++	++	—	—	Mat. gr. mother, mother, sister, 3 mat. aunts	—	Complete	7	
59	♀	23	Child.	+++	+++	++	—	Mother	Brother, urticaria; pat. gr. father, asthma	Complete	6	
60	♀	38	24	+++	+++	—	—	Mat. gr. father, mother, Mat. gr. mother	—			

Abbreviations: child. = childhood.
pat. = paternal.
mat. = maternal.
gr. = grand.

patients. It was notable that the most striking results were obtained in the cases of nurses and other hospital employees who could be closely supervised. However, several cases of complete failure had to be recorded in this ideal group of patients.

It was noted that in some cases psychic upsets played a considerable rôle in precipitating attacks. This is in accord with my experience in asthma.[13]

Protein Sensitivity as Revealed by Intradermal Tests.—The only extensive data hitherto published on protein sensitivity in migraine are by Balyeat and Brittain,[4] and there the methods of testing is not always clear. The following is a list of food and other proteins and the number of cases in which they reacted in our series. These were all tested by the intradermal method described above.

FOODS					
Celery	43	Peanut	16	Cauliflower	8
Pea	41	Cherry	16	Pumpkin	8
Onion	36	Pear	16	Rice	8
Oat	35	American cheese	15	Lemon	8
Lettuce	35	Barley	15	Grapefruit	7
Coffee	34	Tea	15	Sweet potato	7
Carrot	29	Wheat leucosin	14	Pork	7
Casein	25	Buckwheat	14	Egg white	7
Cabbage	24	Rye	13	Cottonseed	6
Banana	22	Plum	13	Hazelnut	6
Cantaloupe	21	Spinach	13	Wheat gliadin	5
Peach	20	Asparagus	13	English walnut	5
Bean	20	Lamb	13	Shrimp	4
Pineapple	20	String bean	11	Whitefish	4
Ginger	20	Black pepper	11	Pecan	3
Strawberry	20	Olive	11	Salmon	3
Apple	19	Lactalbumin	11	Halibut	3
Beet	19	Egg yolk	11	Codfish	3
Date	19	Cocoanut	10	Almond	2
Wheat proteose	19	Fig	10	Wheat glutinin	2
Wheat globulin	18	Rhubarb	10	Oyster	2
Corn	18	Cocoa	10	Tuna fish	2
Radish	18	Potato	10	Sea bass	2
Chicken	17	Cucumber	9	Crab	1
Tomato	16	Beef	9	Lobster	1
Orange	16			Mustard	1

MISCELLANEOUS					
Goose feathers	45	Hog hair	31	Rabbit hair	19
Chicken feathers	44	Orris root	28	Silk	16
Dog hair	43	Canary feathers	27	Tobacco	16
Duck feathers	37	Cat hair	27	Kapok	9
Sheep wool	37	Cattle hair	21		
Horse dander	32	Cotton	21		

These figures do not correspond with those given by Balyeat and Brittain.[4] In their series of tests wheat, milk, eggs, and fish reacted much more commonly while some of the foods which head this list were rela-

tively inactive in their experience. These discrepancies may be the result of differences in technic.

CONCLUSIONS

1. A study of sixty cases of migraine is herewith reported. These cases were studied essentially from the allergic standpoint.

2. In 78 per cent of the cases in which data were available there was partial or complete relief from migraine by the elimination of foods to which the patients were proved sensitive.

3. A study of familial histories shows the incidence of migraine and other allergic manifestations to be high.

4. It is concluded that many cases of migraine are allergic manifestations.

5. Our statistics are in substantial agreement with those published by Balyeat and his coworkers and by Eyermann.

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THE LOCALIZATION AND SPECIFICITY OF CELLULAR SENSITIZATION*

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THE symptoms occurring as a result of a specific sensitization assume many clinical forms, that is, hay fever, asthma, eczema, etc., and one or more of these may be present in the same individual. Patients with allergic diseases are usually multiple sensitive and in them phenomena induced by each allergen is usually the same. This variable response to the same reactor in different individuals and its specificity in each case is considered as related to clinical allergy.

A correlation of the findings obtained by skin testing with the symptomatology and clinical course of these diseases indicated that (1) it is not possible to determine the presence or degree of clinical sensitivity by the skin tests. (2) Certain atopens are more apt to cause one form of allergy but the location of cells specifically sensitive, and not the nature of the exciting agent, is responsible for the variation in symptoms. (3) The clinical features of a sensitization may vary with the dosage of an allergen as seen in the hay fever patient who experiences hives, asthma and abdominal cramps following an overdose of pollen extract. (5) The response to scratch and intradermal tests may be constant in some patients, while in others it varies not only in occurrence but also in different areas or in the same location on repeated testing. (6) Cutaneous testing is accurate most often in hay fever cases and least in eczema and urticaria.

These observations indicate that skin sensitization as determined by cutaneous testing is one manifestation of allergy and that it is not necessarily dependent upon or related to other types.

The discrepancies between skin reactions and clinical hypersensitiveness has received the consideration of many workers, especially Coca,[1] Alexander,[2] Bloch,[3] and Vaughan.[4] Coca attributes the various clinical forms of sensitization to an "atopic state" of different shock organs. This infers that the sensitized cells are capable of reacting in such a way as to present one or more clinical forms of allergy. That this "atopic state" is one of degree is shown by the multiplicity of symptoms following an overdose of an antigen.

Bloch[5] in his definition of allergy has stressed two points. (1) That certain groups of cells (organs) become capable of reacting to a product with the formation of cellular fixed antibodies, and (2) the pathogenesis

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of the reaction is that of an antigen uniting with its specific cellular fixed antibody. The proof of this process is not established beyond a doubt.[6] Secondary to this combination there is a disturbance of cellular equilibrium which usually results in an inflammatory reaction.

Both of these theories purpose to explain the clinical observation that allergy is distinctly a localized process.[7] This may be evident in one disease. Some hay fever patients have itching of the eyes, others itching of the nose, while some have rhinorrhea without any irritation.

The localized feature of allergic reactions is influenced by several factors, heredity being the most important. The hereditary factor is seen in the higher incidence of the same allergy in successive generations as compared to the other forms.[8] We[9] have pointed out this fact in a recent paper on headaches due to specific sensitization. Of lesser importance is the excitant, although as a rule pollen-sensitive individuals are more apt to have hay fever, while those sensitive to animal danders suffer more often with asthma. The period of contact probably accounts for this difference. Whether atopens are inhaled, ingested or act only by contact determines to a great extent what cells will become hypersensitive to members of these several groups. Thus reactions due to inhalants are practically limited to the respiratory tract; ingested excitants affect many tissues, but especially the gastrointestinal tract and central nervous system. Products that cause symptoms by contact are prone to affect exposed areas.

The variation in clinical allergy due to the localization of cells specifically sensitive is well illustrated in cases of skin eruption. The degree of sensitization is not uniform in the glabrous skin, and may occur in a fixed area. In these different areas it may affect only the epidermis, the superficial cutis, or deep cutis. Sulzberger[10, 11] has called attention to this and mentions among others, "The sharply demarcated bluish, fairly deep seated reaction of phenolphthalein, the succulent wheal of urticaria and the blistering weeping erythematous reaction of contact dermatitis."

Of the forms of hypersensitiveness responsible for skin eruptions, the atopic and contact type deserve further mention because the cells specifically sensitive differ as well as the immunologic mechanism. Patients whose eczema is atopic may have positive scratch and intradermal tests, but rarely have specific reactions with patch (contact) testing. In those with skin reactions passive transfer may be accomplished. In these patients other allergies are often present, and a family history of such diseases is frequently obtained. In contradistinction to this, patients with contact dermatitis have neither scratch nor intradermal reactors that are specific for the cutaneous symptoms. The incidence does not depend on a hereditary influence. According to Coca[12] passive transfer has not been successful. Cole[13] recently reports such transfer in primrose sensitization and intimates that Bloch and Jadassohn are us-

ing it routinely in such cases. We have never been able to make transfer in contact cases. The patch test at present is the only means of determining etiologic substances in these cases. The existence of both types of sensitization is to be considered in every case of dermatitis.

One of us [14] has reported the findings in a case of contact dermatitis due to *Helenium microcephalum D. C.* that illustrates the localization of reaction. They were: (1) Scratch and intradermal testing with the water soluble fraction of this plant were negative, while (2) the same material applied by contact produced a local reaction (erythema, vesiculation, edema) and a systemic one with headache, nasal congestion, and abdominal cramps and diarrhea. (3) Passive transfer could not be accomplished. These findings denote that the sensitized cells were limited to the epidermis. Secondary to the changes in these cells a toxic product resulted and on being absorbed produced a general reaction.

A differentiation of atopic and contact dermatitis cannot be made in all cases, by the morphology of the presenting lesion. There is no doubt that many cases of contact dermatitis have been considered as atopic eczema, because on testing with scratch and intradermal methods reactions have been obtained and were considered specific. It is questionable if the reports on the incidence of these tests in cases of eczema are of much value except in those instances where the possibility of contact sensitivity has been considered and worked out in detail. We have seen many cases of eczema respond to food elimination, only to recur in their original severity until the contact cause was eliminated. Unless there is clinical proof one should not assign as etiologic those agents that give scratch and intradermal reactions in cases of eczema. White and Taub[15] have reported that elimination of foods giving skin reactions affects favorably the clinical course of nonatopic cutaneous diseases. One of us[16] has reported this effect in cases of contact dermatitis.

In tissues other than the skin there are sharply circumscribed groups of sensitive cells that account for definite symptoms. It will not be necessary to mention these in detail, but they are illustrated by the effect produced in different people all sensitive to wheat. In one there will be iritis, another experiences episcleritis, a third dysuria and frequency, and others suffer attacks of vertigo, headache with visual disturbances or pruritus ani. While the site of reaction accounts for peculiar symptoms in each case, it is to be remembered that in all cases there are varying degrees of a general or systemic reaction, and the latter may exist at times without symptomatic evidence of the local sensitization.

SPECIFICITY OF REACTORS

In cases with several allergic manifestations and multiple sensitivities, there is a specificity of reactors, that is, certain exciting agents induce the same symptoms on each occasion, the dose being constant. The fail-

ure to consider this feature is evident in the statement that if repeated tests are made the etiologic factors could be found. Even if an extract would give a skin response in every instance of clinical sensitivity it would still be impossible to make the diagnosis of specificity in patients with more than one allergic manifestation. The diagnosis of this phase of allergy is determined only by clinical testing. This problem is illustrated in the case of a patient with hives, hay fever and contact dermatitis who consulted us. In his case eighteen food extracts and the pollen of the three ragweeds gave reactions by scratch tests. Patch (contact) testing was positive with five plants common to his home. On clinical testing two foods produced hives, the dermatitis was due to contact sensitivity to *Helenium microcephalum*, and hay fever occurred only during the pollinating season of the ragweeds and was uninfluenced by foods, etc.

It is common for patients to complain of the severest or recent symptoms and overlook others. In one such patient who suffered from sick headaches and other allergies, there were skin reactions to the extract of grape, cherry, corn, apple, onion, pecan, goose feathers, orris root and wheat. On completion of his diagnosis it was found that very small amounts of apple and pecan would produce a severe form of headache with each ingestion. It was important, therefore, to keep these foods out of his diet. It was also shown that grapes would cause hives, while gastrointestinal symptoms resulted from corn and cherries. Symptoms of vasomotor rhinitis occurred after contact with orris root, goose feathers, and with an excess of wheat in the diet. To have treated him by the elimination of all reactors, because of his present complaint, headache, would have been undesirable, because (1) the treatment of allergic diseases should be as specific as the cause, and (2) unnecessary eliminations are a hardship for the patient. There are, of course, many reasons why this ideal is not always obtained.

The following case reports illustrate the subject of our discussion:

CASE REPORTS ILLUSTRATING SPECIFICITY OF REACTORS

CASE 1.—Male, aged thirty-five, seen because of attacks of tinnitus auris, vertigo and nausea. He also experienced nasal congestion and a constricted feeling in the throat at irregular periods during the summertime. He was skin sensitive to a large number of foods. Clinical testing demonstrated that milk was the cause of his vertiginous attacks, while the nose and throat symptoms were due entirely to muskmelon and casaba. He has remained free of all symptoms by elimination of these three foods.

CASE 2.—Female, aged twenty-eight, came because of nasal congestion, sneezing, abdominal distress, and what she described as "a tired draggy feeling." Of the many reactors it was found that cabbage and cherries would cause abdominal cramps and nausea every time they were taken. Grapefruit, apple and pineapple could be taken occasionally, but when used repeatedly in the diet, produced similar symptoms, though less severe. All cold drinks would cause identical symptoms. Hot tea or

coffee gave no trouble but if taken daily, or in large amounts, would result in what she described as a "tired draggy feeling."

CASE 3.—Male, aged thirty-eight, suffering with symptoms of hay fever and colitis. He was skin sensitive to thirty-five foods. Trial diets demonstrated that the legume group would cause symptoms of colitis. The other foods were of no clinical importance.

CASE 4.—Male, aged thirty-five, referred because of coated tongue, abdominal distress, gas, bloating, attacks of diarrhea with mucus and pruritus ani. He also had chronic nasal congestion, watering of the nose and sneezing while working at an institution where eggs constituted a frequent article in diet. On testing, egg extract gave rather large reactions. They were eliminated along with several other foods and feathers. The symptoms abated within four or five days. On clinical trial the patient reported the occurrence of all symptoms enumerated above when egg was tested. With several other foods only abdominal symptoms were noted. Feathers produced nasal congestion and sneezing.

COMMENT

In Case 1 there were two groups of cells clinically sensitive, and in each instance the exciting agent was specific for that one organ. In the second case the site of reaction was in the gastrointestinal tract, and there were multiple specific reactors. There are two other features of this case that should be considered. (1) Wheat produced signs of a systemic reaction, without evidence of a local one, and (2) physical agents produced symptoms similar to food allergy. In our third patient we have an excellent illustration of localized sensitization to a genetic group of foods. This classification suggested by Vaughan[17] is of definite value in dietary management in many cases. In our last case there were numerous groups of cells sensitive to egg. This patient was hyperallergic and it has been observed that these individuals respond in many tissues to the same etiologic factor. This case suggests that while the symptoms vary with the localization of reaction, the mechanism responsible for the pathologic changes exists in varying degrees in many tissues.

Since clinical allergy is manifested by various localized processes, cutaneous tests will be of value in those cases where these groups of cells (organs) and the skin are sensitive to the same allergen at the same time. Vaughan[18] has reported approximately 50 per cent satisfactory results from skin testing. This percentage is to be expected, when we consider that we are dealing with organs of different embryonic origin, histologic structure and immunologic properties. In view of these facts, some men have practically discarded skin testing. Any laboratory procedure that will give one such a large amount of information should not be discarded because of shortcomings. It is best to use the various tests to their full advantage and then supplement them with elimination diets, addition diets, etc., to determine all etiologic factors and their specificity. Dietary manipulation is not without fault, especially in eczema and headache cases. It is quite distressing in these patients, because symp-

toms cannot be relieved as in hay fever and asthma. Symptoms other than those due to allergy are relieved by elimination diets, and this fact should be considered in making an etiologic diagnosis.

It is apparent, therefore, that a patient cannot be tested by laboratory methods alone to determine the clinical sensitizations, and it is unjust to the patient to create this impression. In every case it should be thoroughly understood that clinical testing is part of the diagnostic procedure. In those who obtain relief by treatment based on skin sensitivities the diagonsis of specificity should be made so that treatment may be carried out on an etiologic basis.

Reports concerning allergic diseases should indicate if the sensitizations reported are clinical or cutaneous. In the latter case it should be stated if they are determined by scratch, intradermal or patch. In cases of eczema or dermatitis this is especially important, and in addition the type of hypersensitiveness responsible for symptoms should be given, when known.

The subject matter of this paper is not new. It has been presented at this time because we believe this topic to be one of the fundamentals of allergy, and well worth our consideration.

CONCLUSIONS

1. The same exciting factor can produce many forms of allergy, depending on the localization of cells specifically sensitive. One or more of these forms may occur in the same patient, due to one or several allergens.

2. Skin tests when positive indicate skin sensitivity only. They are one form of allergy, not necessarily related to the others.

3. Sharply circumscribed allergy is best illustrated by skin eruptions. It may be limited to definite areas, or to certain groups of cells in several locations. This may be due to atopic or contact hypersensitiveness.

4. Skin testing is not a determination of clinical sensitivity, therefore it should be supplemented in every case by clinical testing.

5. Specific elimination is the therapeutic ideal.

6. In case reports it should be stated whether the sensitivities are cutaneous or clinical.

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(For discussion, see page 605.)

THE MANAGEMENT OF THE DUST ASTHMATIC*†

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ALTHOUGH it has been recognized that the majority of asthmatics have symptoms due to hypersensitiveness, the determination of the exciting substance, of its origin and nature, is not simple. Many substances have been implicated from time to time. One of the most common is the unknown substance in house dust. Others arise from animal emanations and some from products which go into the manufacture of household articles. It is therefore very important to have a wide knowledge of the substances to which atopic individuals may react and the many sources from which they are derived. Feinberg[1] recently listed the uses to which animal hairs and vegetable fibers are put in industry.

It was Kern[2] who first called attention to house dust as a cause of asthma. Cooke[3] and Rowe[4] demnostrated sensitivity to dust in more than 40 per cent of the patients they tested. One of us[5] reported nineteen cases of asthma due to dusts from mattresses who did not react to cotton or kapok, the substances of which the mattresses were made. The two hundred cases from which the nineteen were selected had been edge of the substances to which atopic individuals may react and the asthma. Cooke[3] and Rowe[4] demonstrated sensitivity to dust in more tested with extracts of dust either from the floor sweepings or materials taken from the vacuum cleaner bag. These nineteen cases did not react to these extracts, but did react to dust collected individually from their bedding. This would indicate that reactive dust is found more often in furniture than in floor coverings, and shows the necessity for the collection of individual dust samples. For the past six years we have collected dusts in the following manner:

The cloth bag is removed from the vacuum cleaner and the machine allowed to run for a moment in order to free the mechanism of old dust. A piece of muslin cloth is tied over the air outlet, and a sample is taken from the patient's bed. Similarly, samples are taken in new pieces of muslin from each other bed in the house, each grouping of furniture, and each rug and carpet. In addition, samples of dust are obtained from the automobile and from the working environment. Each sample is placed in a wide mouthed bottle, covered with Bernton's fluid and allowed to stand at room temperature for forty-eight hours. The supernatant fluid is used without filtration for scratch tests. If intradermal tests are necessary in the absence of positive scratch reactions, the solutions are run through filter paper and then through Seitz or Berkefeld

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filters, and the filtrate is used diluted 1:10 to test patients by the intradermal technic. Most patients give good reactions to the extracts by the scratch method.

Table I illustrates the high average of dust sensitive individuals in this part of the country, and the more common sources of this dust. Patients may be sensitive to dusts from more than one source.

TABLE I
INCIDENCE OF DUST SENSITIVE CASES AND SOURCE OF DUST

TOTAL CASES GIVING SKIN REACTIONS	REACTIONS TO DUST	MALE	FEMALE	AGE	SOURCES			
					BEDDING	FURNITURE	RUGS	MISC.
1250	250 or 20%	105	145	1 to 69	145	105	95	45

The large number of patients who are sensitive to dust makes it second only to pollen as a cause of symptoms and demonstrates the importance of locating the exact source of contact with it in the patient's environment before he is dismissed as an "incurable," "hopeless" allergic or consigned to the already overburdened class of bacterial sensitive individuals, for whom at present little can be done.

Preparation of dust extracts as described above has resulted in improvements both in diagnosis and treatment. The reasons are apparent when one studies Table I and notes that the majority of reacting dusts are found in bedding and overstuffed furniture and not in rugs and carpets, unless these have become contaminated from beds or overstuffed furniture. Mose of these sources of dust would have been overlooked if extracts had been made only from the floor sweepings contained in the vacuum cleaner bag.

The following case demonstrates the necessity for the collection of individual dust samples.

The patient, F. M., white, a boy of fifteen years, came to us December 7, 1929, with a history of continuous asthma of five years' duration, with very marked winter exacerbations severe enough to confine him to bed for months. His family and past histories were negative for allergy.

Examination showed a markedly undernourished boy with a typical asthmatic habitus, who weighed 90 pounds. He was pale, dyspneic and very cyanotic. The chest was increased in all diameters; there was marked emphysema. The heart, abdomen and limbs showed no abnormalities. Scratch testing revealed suspicious reactions to egg, grapefruit, prune, apricot, mutton, onion and spinach and a very large reaction to our stock dust. Individual dust samples were requested and the following were brought: dining room carpet dust, living room carpet dust, bedroom carpet dust. These were extracted and used for scratch tests which gave negative reactions. Since it is very unusual to find negative reactions to dusts from the patient's environment when large reactions have been obtained to our stock dust, we suspected that the real sources of dust had been overlooked and therefore requested a more thorough collection of dust from his home. Extracts of the second group of samples gave the following reactions: neighbor's home ++, brother's mattress and pillows ++, parent's pilows and mattress ++, boy's mattress and pillows ++, pine

pillow 0, sitting room lounge 6+. Dust precautions were instituted and treatment with dust extract was started. Within four weeks improvement was very noticeable, and in two months he was free both of acute attacks and of wheezing and so remained free during a ten months' period of observation. He was seen again March, 1932. He had had no asthma in the interim.

This case was selected because it is a very typical one and because it emphasizes the necessity for cooperation of the patient in collecting dusts properly.

Once dust has been implicated as a cause for symptoms and its source discovered, treatment can be planned intelligently. Since the complete avoidance of house dust contact cannot be maintaineed under ordinary living conditions, it is necessary to prepare a relatively dust free sleeping room for the patient, to eliminate from the house as many as possible of the articles containing active allergenic dusts, and to raise the tolerance to dust by parenteral injections.

The following instructions for the preparation of a dust free room are given to the patient:

1. Your room may contain only one bed, preferably an iron one. It must not have a box spring.

2. All the furniture, rugs, curtains, drapes must be taken from the room, clothes closets emptied and the room cleaned as follows:

(a) Seal all of the furnace pipes leading into the room. Clean the wall paper. Scrub the woodwork and the floors in the room and closets. Wax the floors.

(b) Scrub the bed (this must be done out of the room), set up in the clean room. Scrub the springs (this must be done out of the room), place on the clean bed frame. Cover the mattress and pillows with rubber sheeting (this must be done out of the room, and the entire mattress and the pillows must be covered, the rubber sewed on so as to make it absolutely air tight), bring into the cleaned room and place on the clean springs. Bedclothes must be washed and be of material that will stand washing often.

(c) A wooden chair which has been scrubbed may be used in this room. Rag rugs which can be washed at least once a week may be used on the floor. Plain light curtains which can be washed once a week may be used on the windows.

(d) This room must be cleaned thoroughly once a week.

3. You must sleep in this room, all dressing and undressing must be done elsewhere in the house.

Articles of furniture which contain allergenic dusts which can be dispensed with should be removed from the home. If it is impossible to do this, each article should be vacuumed thoroughly daily and at a time when the patient is away from the house. Following the vacuuming the house should be aired thoroughly. The patient should be warned against sitting in or lying on chairs, couches or beds which contain these dusts. In this way much dust contact is avoided, but since very sensi-

tive patients may still have symptoms from unavoidable residual contacts, or from similar dust contacts in other houses, it is advisable to attempt to raise the tolerance to dust by injections of the allergen.

We find it safe to begin treatment with 0.1 c.c. of a 1:50 dilution of reacting dust in Bernton's fluid and that doses of 0.5 c.c. of the concentrated extract usually suffice to protect the patient who has faithfully followed the foregoing recommendations. When the maximum dose has been reached and the patient is symptom free, we continue this dose at monthly intervals for from six to twelve months. More than 75 per cent of patients who become symptom free following these procedures remain symptom free after treatment with dust is discontinued unless there are other sensitivities of clinical importance.

In this connection we have observed the following interesting facts: When we obtained feathers for the preparation of feather extracts from a mattress and pillow renovating company, we found many patients who reacted to our extracts. Since we have obtained feathers plucked dry from the fowl, our feather extracts have given many fewer reactions, and we have determined that many of the former reactions were due to dust contamination of feathers at the source of supply.

Each spring we see a number of dust sensitive asthmatics who have severe symptoms of a week's duration in early April. They are not sensitive to tree pollen but on investigation are found to have been exposed to unusual amounts of dust because of the spring house cleaning activities.

SUMMARY

1. The unknown substance in house dust is a very common cause for symptoms in asthmatics.

2. It is found more commonly in mattresses, pillows and overstuffed furniture than in floor coverings.

3. It is imperative to locate the sources of these dusts in the patient's environment and to eliminate them as well as all other factors if the symptoms are to be controlled.

4. Methods for accomplishing this end have been outlined.

5. When these methods are adopted and carried out, treatment of the dust asthmatic is equally as satisfactory as that of the pollen asthmatic.

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10616 Euclid Ave. *(For discussion, see page 611.)*

A SUMMER DERMATITIS CAUSED BY A COMMON WEED*

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THE cutaneous response to substances which come in contact with the skin directly or indirectly, varies greatly. Fortunately most of us possess protective barriers which prevent our skin from giving any noticeable response, but evidence is gradually accumulating to prove that under certain circumstances these barriers may fail to protect, and the once immune skin may become very sensitive even to the minutest trace of some irritating substance that reaches it either by direct contact or through the blood stream. The lesions produced are variously known as eczema, dermatitis, contact eczema, contact dermatitis, etc., and different schools of dermatologists use one or the other of these terms, some using them interchangeably. Without entering the discussion as to the choice of these names, we will use the word "dermatitis."

Specific skin lesions in susceptible persons are caused by many different substances, for example, in plants as primrose, *rhus*, etc., in foods as milk, wheat, etc., in drugs and chemicals as iodides, phenolphthalein, nickel, etc., in animal emanations as dandruff, hair, etc., and so on. It has been stated that any substance may become an irritant to some person. We wish to describe an irritant that we have not found recorded in literature, although there are a few references to somewhat similar irritants.

In 1831 Elliotson[1] wrote the following about one of his patients: "On handling the flowers of grass, her hands always became instantly inflamed; therefore, there is clearly in her skin a peculiar susceptibility to irritation from the flowers of grasses."

In 1874 Blackley[2] demonstrated that a dermatitis was produced on his scalp and face if he wore a hat containing the rye plant in full bloom.

In March, 1919, Hannah[3] in a paper on "Ragweed Dermatitis," described the lesions in a woman of forty-nine occurring at first only in summer and later being present all the year, especially when working in the field. Intradermal tests with pollen extracts were positive. He treated her successfully by giving injections of pollen extract.

Later in the same year, 1919, Sutton[4] described four cases of summer dermatitis in farmers. No one of these had typical symptoms of pollen disease. At least three of these were tested with the extracts of pollen or with macerated pollen, and gave positive skin reactions. In one

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†From the John McCormick Institute for Infectious Diseases, Chicago, and The Allergy Clinic, University of Chicago Medical School.

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of these patients, the inhalation of ragweed dust caused the characteristic dermatitis of the skin, while the ingestion of the pollen and leaves had no effect. One of these patients was treated by Dr. Duke. Three of them were treated successfully with the extracts of ragweed pollen. In the discussion of this paper, Dr. Lain of Oklahoma City suggested that the dermatitis might be due to a glucoside introduced by the hairs on the plant itself and not to the pollen.

Since 1919 several other reports of ragweed or pollen dermatitis have appeared. Duke,[5] in his book, shows a picture of a dermatitis produced by placing a flowering branch of ragweed on the skin. He suggests that each of the numerous small lesions is due to contact with a pollen grain.

Sulzberger and Wise,[6] in 1930, reported a case of dermatitis during August and September in a salesman, age forty. He gave negative skin tests by the scarification method with pollens of common grasses and weeds, but gave a marked twenty-four-hour contact reaction with the pollen of the small ragweed. From June to August, he was treated with x-ray and lotions, with no results. Then a series of intracutaneous injections of pollen extracts were given, with excellent results.

In 1931, Brown, Milford and Coca[7] described two such cases. A male, aged fifty-two, had had an itching rash from May to late summer. Intradermal tests with proteins gave negative reactions. The aqueous extract of ragweed pollens gave a questionable reaction. Scratch tests with the ethyl ether extract of ragweed pollen gave no immediate reactions. Patch tests with the same oil gave, after six days' exposure, a severe local rash, accompanied by an exacerbation of the generalized itching.

A second patient, male, aged thirty-eight, had had late (?) hay fever since June (?) for seven years, and during the last three years had had a generalized skin eruption from August to frost. He gave a marked local reaction to the ragweed pollen extract and a marked immediate reaction with the ethyl ether extract of ragweed pollen. Patch tests with the same oil, after seven days, reproduced his skin eruption.

One of these patients was treated successfully with injections of a preparation made from this ether soluble fraction.

In 1930 Bengtsson[8] reported some work with Dr. Chobot but the abstract of this paper did not give the details of the work. However, she did test with alcoholic extracts of the leaf as well as with the pollen oil.

The description of our cases is as follows:

The first patient was referred to the Allergy Clinic of the University of Chicago by Dr. Becker of the Dermatological Clinic.

A brick mason, aged sixty-two, had lived in the southern part of Chicago for many years. He had never had hay fever or asthma. In August, 1927, he first noticed an itching dermatitis of the face, which persisted for one month. Each fall, from 1928 to 1930, the dermatitis recurred and each year persisted for a longer period. We first saw him in 1930 with a dermatitis involving the skin of the face, neck, and

wrists. Scratch tests with all common contactants, including pollens, were negative, after fifteen minutes. As his skin was improving, he did not return in 1930. In June, 1931, the dermatitis recurred and he reappeared at the clinic in August with an acute exacerbation of his trouble so violent that he was hospitalized. (Fig. 1.) Scratch tests with all common contactants were repeated and no immediate reactions were found. Two days later a roughening of the skin was noted at the site of the test with the pollen of the burweed marsh elder. Twenty-four-hour patch tests with the pollens of large and small ragweeds, burweed marsh elder, and sunflower gave

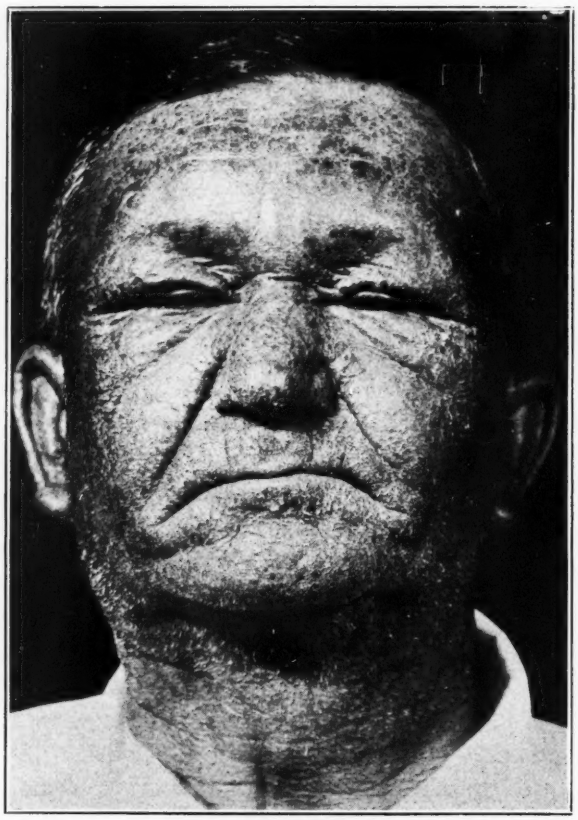

Fig. 1.

no reactions except for that of the burweed marsh elder, which produced an erythematous vesicular patch, 2 cm. in diameter, which persisted for several days.

At this time a second patient, male, aged fifty-five, with a very similar history was referred to the Allergy Clinic by Dr. Obermeyer of the Dermatological Clinic. Similar tests were done on these two patients and their reactions throughout were analogous. As the onset of the dermatitis in both preceded by several weeks the pollinating time of the burweed marsh elder, contact tests were made with 5 mm. square pieces of the leaves of several common weeds. Twenty-four hours later these patients reported in the clinic with violent vesicular oozing reactions, 3 to 4 cm. in diameter, at the site where the leaf of the burweed marsh elder was applied. There was no reaction with the leaves of the large and small ragweed, sunflower and cocklebur. These lesions required dressings for three weeks.

In October the desiccated leaves of the burweed marsh elder were extracted with water, physiologic saline, 20 per cent alcohol, and anhydrous ether. All tests made with these extracts by the contact method gave, within twenty-four hours, definitely positive reactions, that of the ether extract being much more violent. Anhydrous ether extracts of the desiccated leaves of the sunflower, large and small ragweed, and the burweed marsh elder and of the pollens of each of these gave positive reactions only to the extract of the leaf and pollen of the burweed marsh elder. The toxic principle of the burweed marsh elder leaf was completely removed by ten extractions with ether, as ninety-six-hour exposure by contact test with the leaf thus treated gave no reaction. An absolute alcohol extract of the dried leaf was diluted to 60 per cent by weight with water and shaken three times with petroleum ether, thus removing chlorophyl, fats, sterols and doubtless other lipoids. Almost all of the activity remained in the alcohol layer. Likewise the activity remained behind after shaking with animal charcoal. Further chemical studies are in progress.

We are planning to treat these patients with an extract of the leaf prepared according to Spain and Cooke's method of making extracts for the treatment of poison ivy dermatitis.

The *Iva xanthiifolia* has the following common names: "burweed marsh elder," "giant poverty weed," "false ragweed," and "careless weed." It is an annual composite and, until flowering time, resembles the *ambrosia trifida* in size and leaf outline. The yellow flowers produce an enormous amount of pollen and seed. It grows abundantly in rich moist soils in certain sections of our midwestern states north of Texas and pollinates during August and September.

DISCUSSION

In a review of these reports in the literature on so-called "pollen dermatitis" and "ragweed dermatitis," we find such a great variation in the symptoms, the duration of the symptoms, the methods of testing for specificity, the materials used in specific treatment, and finally in the methods of treatment that we must conclude that all these dermatoses do not fall in the same group or that the causative agents may differ or that the diagnosis was only partially correct. The first case of pollen dermatitis to which reference is made in the literature is that described in 1831 by Elliotson. If his is to be called a pollen dermatitis, we should call all of the reactions in those who give positive reactions to our pollen tests, pollen dermatitis.

Blackley's response to pollinating rye probably falls in the same group as Elliotson's case.

The cases reported by Hannah and by Sutton were chronic and gave immediate positive reactions to pollens or pollen extracts by scratch or intradermal test.

The cases reported by Sulzberger and Wise and one of those by Brown were chronic and gave no immediate reactions to pollens or pollen extracts by scratch or intradermal tests. Contact tests with pollens or pollen oil gave, within twenty-four hours to three weeks, typical local skin lesions.

There is, therefore, a marked difference in the dermatitis as described in these reports.

It is hard to explain also the successful results in the treatment of these patients. Hannah and Sutton had successful results with lipoid-free pollen extracts. Sulzberger and Wise were successful with the Lederle pollen extract, which may contain some of the pollen lipoids. Brown, on the other hand, had successful results by using the pollen lipoids alone.

CONCLUSION

The demonstration that the burweed marsh elder, a common weed in many sections, contains a toxic principle that is the specific cause of a dermatitis in two patients from a small group suggests that there may be many unrecognized cases due to the same cause and that many other common plants also may be a specific cause in certain cases.

The toxic principle affecting these patients can be removed from the leaf and pollen by ordinary lipoid solvents and can be freed from fats, sterols and chlorophyl without appreciable loss of activity.

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(For discussion, see page 605.)

PERSISTENT ANGIONEUROTIC EDEMA*

Report of a Case

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THE criteria of Quincke's edema as described by Quincke himself and other authors emphasize the fleeting occurrence and recurrence of this phenomenon. The duration as a rule varies between several minutes and several days. A persistence of the condition exceeding this length of time is very rare, and the extensive literature on the subject of Quincke's edema records but a few such cases. The first physician in the twentieth century to describe persistent angioneurotic edema, or as he calls it "chronic trophedema," is Dr. Meige,[1] a pupil of Charcot. The medical profession of his time, far from suspecting the allergic nature of this disease, believed it to be a symptom of hysteria. To cite this author: "On connut aussi les oedemes hysteriques: l'oedeme blanc, l'oedeme bleu, et le trophedeme chronique. Ces troubles vasomoteurs et trophiques ne sont que les products de la simulation." Schalit[2] mentions three particularly interesting cases of edema of the left masseter, facial and temporal muscles followed by a compensatory hypertrophy of the muscles of mastication of the right side. Although the author realized the allergic nature of the condition, skin tests for determination of the etiologic antigen were not done. Dr. Schalit, however, showed that infection of the teeth, gums, etc., played no part in causing the edema.

Cassirer and Hirschfeld[3] mention the occasional occurrence of persistent angioneurotic edema of the eyelids. Radimska and Jandowa[4] also describe a persistent form of Quincke's edema, which they call "Dauer-oedem." An unusual case, described by E. Melkerson,[5] is that of a thirty-five-year-old man who had suffered from recurrent angioneurotic edema of the lip associated with relapsing attacks of facial paralysis since his eighth year. When the patient was eighteen years of age, the facial paralysis became permanent as did the swelling of the lip.

CASE REPORT

A fifteen-year-old Porto Rican boy was admitted to the hospital on April 25, 1931. He had been in good health until April 10 when he started to complain of pain in ankles and knees, later on in elbow and shoulder joints. He also began to notice a swelling of the upper lip and nostrils. His family history was irrelevant. None of his blood relatives—as far back as the third generation had had at any

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time urticaria, Quincke's edema, asthma, hay fever or migraine. His personal history is as follows: pneumonia at age of ten years, tonsillectomy when twelve years old. There was no history of previous attacks of polyarthritis or previous occurrence of allergic manifestations. The general examination disclosed angioneurotic edema of the upper lip and nostrils. There was evidence of mucopurulent discharge on the posterior pharyngeal wall, and the x-ray picture of the sinuses revealed a thickened mucosa of the left antrum. The sinuses were washed three days later but the return was clear. The submaxillary lymph nodes were slightly enlarged. The heart was not enlarged but there was x-ray evidence of accentuation of right and left auricular curves. The apex beat was heaving and in the fifth interspace. There was a blowing systolic murmur transmitted to the axilla and a harsh diastolic murmur to be heard at the apex. P2 was louder than A2. A blowing diastolic murmur was heard at the base over the aortic area. The rhythm was a regular sinus rhythm. The electrocardiogram showed a sinus arrhythmia. There was no deviation of the electrical axis. The spleen and liver were not enlarged. A pistol shot murmur was heard in the groin. The following joints were tender and swollen: both elbow joints, right knee joint, both ankle and both hip joints. The Wassermann test, colloidal gold, blood chemistry, and urinalysis were negative. The blood count revealed a hyperleucocytosis of 17,000. There was an eosinophila of 2 per cent. The feces were negative for ova and parasites. The diagnosis of active rheumatic heart disease with mitral and aortic insufficiency, and regular sinus rhythm, and of rheumatic polyarthritis was made.

In the hospital the patient had a monocyclic course followed by a subfebrile stage. Beginning on April 27 the patient was placed on salicylate medication. The medicine was discontinued on May 13, 1931. On June 19 the patient was temperature free and remained so thereafter. The pain and swelling of the joints had disappeared. The leucocyte count had subsided to an average of 6,500 (blood counts were taken twice a week). There was, however, a persisent eosinophilia ranging from 2 to 12 per cent in the various counts. The edema of the upper lip still persisted.

The patient was skin tested with 115 different antigens. Both the scratch method (dry powdered proteins from the Arlington Chemical Company) and the intradermal method (solutions with known nitrogen content—Coca) were employed. The patient was tested for bacterial allergy with 0.02 c.c. of freshly prepared filtrates of *Staphylococcus aureus* and *albus*, indifferent green and hemolytic streptococci, and with 0.02 c.c. 1:10,000 O.T. Since there exists a group reaction to nematodes, ascaris antigen was used for determination of allergy to intestinal parasites. Two-hundredths c.c. was injected intradermally. The skin tests were negative excepting for a one-plus immediate reaction to ascaris antigen, a two-plus reaction to O.Tub. on June 15, 1931, and a two-plus delayed reaction with necrotic center to *Streptococcus hemolyticus*. The date of this was June 12, 1931. There was, however, no recurrence of pain in his joints, nor was there any apparent change in his angioneurotic edema. The Prausnitz-Küstner[6] passive transfer was not attempted. On June 20 and June 27 ova of *Trichocephalus dispar* were found in the feces, the previous examinations having been negative. On July 2 anthelmintic treatment was begun with disappearance of ova in the feces. On July 15 the patient was discharged to the allergic clinic. He was feeling well and had no complaints. His blood count showed an eosinophila of 4 per cent. The edema of the upper lip had subsided considerably but a persistent thickening remained clearly visible.

On the patient's last visit to the clinic on October 15 this thickening still persisted, although he had not had in the meantime any further attacks of polyarthritis, or increased swelling of his lip. The feces at this time showed no ova on repeated examination.

The points of interest in this case are the persistent angioneurotic edema and the question of whether the etiologic factor of this condition was bacterial allergy or hypersensitiveness to *Trichocephalus dispar*. It seems that the infiltration of his lip would have subsided simultaneously with signs of activity in the patient's joints had it been due to bacterial allergy. Furthermore, one would not be able to account for the retrogression of the Quincke's edema following institution of anthelmintic treatment. Unless one assumes that the patient's rheumatic infection had continued to be active although no apparent signs of activity persisted at the time the anthelmintic treatment was given, it would be impossible to explain the condition on the basis of bacterial allergy. On the other hand, it must be borne in mind that allergic manifestations occur rarely[7] in persons actually harboring helminthic parasites, and are more common in those who handle the parasites but are not actually infested with them.[8, 9] With these possibilities in mind it seems pertinent to mention a case described by Huebschmann[10] in 1894 who presented an angioneurotic edema persisting for three months, associated with rheumatic polyarthritis and facial paralysis. He believed that all these manifestations had an identical etiologic factor. Rosenthal[11] described several similar cases.

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ASTHMA DUE TO YEAST (BY INGESTION)*

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YEASTS and molds as a causative factor in bronchial asthma have recently been emphasized, especially by von Leeuween[1] and Bernton.[2] They are present in dust and in this manner are frequently inhaled, with the production of asthmatic symptoms. Yeast as an allergen, present in food and causing asthma by its ingestion, is not of common occurrence, judging by its infrequent mention in the literature. Yeast is also recommended as a medical agent for numerous symptoms and diseases, and it is surprising that more cases of asthma due to this substance have not come to our attention.

CASE REPORT

The patient, A. K., a boy five years old, gives the following history.

He was breast fed one month, then bottle fed. At the age of one year he developed a generalized eruption for which many food modifications were attempted. Later he developed continuous nasal discharge and occasional coughing spells. At one and a half years tonsils and adenoids were removed, but the previous symptoms persisted until the age of two and a half years when typical asthmatic seizures were noted. These attacks responded quickly to adrenalin but to no other medication. The child was seen by many pediatricians and otolaryngologists but no relief was obtained. Attacks continued with increasing frequency, and in September, 1930, complete skin tests were made, including all foods, epidermals, pollens and miscellaneous.

A strongly positive reaction to yeast was obtained. All other tests were negative. This was repeated several times with uniformly positive results. Tests made on the parents to yeast were negative. A passive transfer was done on two nonallergic adults and markedly positive reactions were obtained to yeast protein, with both the cutaneous and the intradermal tests.

All foods containing yeast were eliminated from the diet, such as bread, cakes, grape juice and fermented beverages.

Desensitization was started with a 1:20,000 solution of Fleischmann's yeast. Treatment was continued until 0.3 c.c. of 1:100 solution was given. The child was then allowed to eat small amounts of bread. During the course of treatment the general condition improved, and the asthmatic seizures became less frequent and finally ceased. Upon resuming the eating of bread, slight asthmatic attacks were again noted. This also followed on two occasions when small amounts of freshly prepared wine were consumed.

A skin test in April, 1931, still showed a markedly positive reaction to yeast. Because of a return of mild asthmatic seizures in April, 1931, another series of yeast injections was given, and at present he is getting 0.5 c.c. of 1:100 solution and no known yeast containing foods are being given.

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*Read before the tenth annual meeting of the Association for the Study of Allergy, New Orleans, La., May 9, 1932.

Cutaneous tests to yeast:

Fleischmann	++++
Yeast, bakers'	++++
Yeast, distillers'	++++
Yeast, brewers'	++++
Lactose fermenting	++++ (large pseudopods)
Lager beer	++++

Cutaneous tests to molds:

Aspergillus fumigatus	0
Aspergillus alternaria	0
Aspergillus nidulus	0
Aspergillus niger	0
Monilia pencillium	0
Monilia Camemberti and *Roqueforti*	0

CONCLUSIONS

Herein is demonstrated a case of asthma in a five-year-old boy with 4-plus reactions to yeast by the scratch and intracutaneous tests. Passive transfer was done with markedly positive reactions to yeast protein. Omission of yeast products from the diet stopped the asthma which had been present for two and a half years. At present desensitization to yeast is being attempted by the subcutaneous method.

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CERTAIN PHASES OF DIGESTION IN RELATION TO ALLERGY*†

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IT HAS been our effort to study various types of allergy to see whether or not there are any common, underlying factors. This first report deals largely with the study of stools, urine, certain phases of the blood and basal metabolic rates.

We have studied the stools of a selected group of allergic patients from the standpoint of routine stool examination. This includes occult blood, ova and parasites, color, odor, P_H and bacteriology. In our bacteriologic studies we have arbitrarily selected for our culture media one aerobic medium which was blood agar, one medium of lowered oxygen tension which was brain broth and one anerobic medium which was cooked heart. These were selected after a preliminary study of several types of media, and we feel that by these selected media we can culture out most of the organisms seen in a stained smear made from a fresh stool specimen. We are well aware of the fact that there are several others which might have been chosen. Our aim was to get a cross-section of the bacterial flora which could be used as a basis for comparison. The stools studied have been normal passages, and cultures have been taken from thirty minutes to four hours following evacuation. All specimens brought in after four hours have been discarded because of changes which take place within the stool after that time. Aseptic technic was observed, as far as possible, to avoid contamination.

Based on some forty stool examinations from allergic individuals in comparison with a large number of normal stools, we are forced to the conclusion that, as far as we are able to tell, there are no demonstrable differences in the bacterial flora of the allergic and the nonallergic individual. In these studies we were aided by Dr. J. T. Meyers of the Bacteriological Department. The odor of the stools was more acrid, and more fermentative changes were noted in the allergic stools. This was more noticeable as the P_H of the stool tended toward the acid side.

The P_H of the stools from the allergic group showed a definite trend to a low P_H, some of the stools studied having a P_H as low as 5.8. In this work we followed the technic as suggested by Forman,[1] et al., in which they describe three types of stools; the normal having a P_H of 7 to 7.5, the alkaline stool, and the third type, the soft, mushy, gassy stool in

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which the P_H ranged from 5 to 6.5. In our group of normal stools the P_H varied from 6.5 to 7. This method was the colorimetric method, and Mansfield Clark[2] standards were used. Table I reports the findings in the group of allergic cases studied.

TABLE I
STOOL ACIDITY IN ALLERGIC PATIENTS

PATIENT	DIAGNOSIS	STOOL P_H	PATIENT	DIAGNOSIS	STOOL P_H
Mr. M.	Asthma	6.	Miss B.	Migraine	6.4
Mrs. R.	Asthma	6.2	Mr. D.	Eczema	6.4
Mr. U.	Asthma	6.6	Miss L.	Eczema	6.
Mr. H.	Asthma	6.	Mrs. M.	Eczema	6.8
Mr. He.	Asthma	6.6	Mrs. N.	Urticaria	6.8
Babe D.	Asthma and eczema	6.	Mrs. W.	Urticaria	6.3
Mrs. A.	Asthma	6.6	Mr. R.	Vasomotor rhinitis	6.
Mr. Ha.	Asthma	6.4	Mr. J.	Arthritis	6.6
Mrs. D.	Asthma	6.5	Miss C.	Hay fever	6.
Mr. McQ.	Asthma	6.2	Mrs. L.	Hay fever and asthma	6.3

When we were assured that these P_H findings of the stool were consistent, we then began a study of the urinary P_H and obtained a number of specimens from the group of allergic patients whose stools had been studied. We followed the colorimetric method the same as for the stools

TABLE II
URINARY ACIDITY IN ALLERGIC PATIENTS

PATIENT	DIAGNOSIS	URINARY P_H	PATIENT	DIAGNOSIS	URINARY P_H
Mr. M.	Asthma	6.	Mr. D.	Eczema	6.6
Mrs. D.	Asthma	6.	Miss L.	Eczema	6.
Mr. U.	Asthma	6.4	Mrs. M.	Eczema	6.6
Mr. H.	Asthma	6.2	Mrs. N.	Urticaria	6.6
Mr. He.	Asthma	7.	Mrs. W.	Urticaria	5.8
Babe D.	Asthma and eczema	6.	Mr. R.	Vasomotor rhinitis	6.
Mrs. A.	Asthma	5.8	Mr. J.	Arthritis	6.
Mr. McQ.	Asthma	6.	Miss. C.	Hay fever	6.
Miss B.	Migraine	6.	Mrs. L.	Hay fever and asthma	6.

and checked this against the electrometric method in certain cases and found that the difference was negligible. Our results agreed with the findings of Schaefer and Schmidt[3] who found the average P_H of one hundred urines to be 6.33. Table II gives the P_H of the urines of the cases studied.

Following the method outlined by Oriel, et al.,[4] we obtained urinary proteoses to determine whether these could be used in the treatment of the various allergic manifestations. We have been able to obtain urinary proteoses in varying amounts from practically every urine studied. These we made up to 1:1000 dilutions and skin tested the patients. We found only three who reacted positively, and these were made from the urines obtained from patients during, or immediately following, an asthmatic seizure. We were unable to demonstrate an active antigen in any of the urines except those of the asthmatics as stated above. The urines from the eczema and vasomotor rhinitis cases were taken while the patients were having active manifestations.

Gastric analyses were made, and our findings showed a wide range of variation. We were unable to attach any particular value to this procedure, our results varying from no acid to one case showing a free hydrochloric acid of 73.°

The basal metabolic rates were carried out and here, again, we encountered a wide range of variation. Our rates varied from a minus 13 to a plus 53. It is interesting to note that in the patient in whom we obtained a basal metabolic rate of plus 53 there was no acid found in the gastric content, even when these tests were rechecked. Table III shows our results:

TABLE III

GASTRIC ACIDITY IN ALLERGIC PATIENTS

PATIENT	DIAGNOSIS	B.M.R.	GASTRIC HCL		PATIENT	DIAGNOSIS	B.M.R.	GASTRIC HCL	
			FREE	TOTAL				FREE	TOTAL
Mr. M.	Asthma	4	24	67	Mr. McQ.	Asthma	2	40	60
Mrs. R.	Asthma	0	6	16	Miss. B.	Migraine	5	22	38
Mr. H.	Asthma	11	58	79	Mr. D.	Eczema	2	73	111
Mr. He.	Asthma	0	47	62	Mrs. M.	Eczema	6	30	53
Mrs. A.	Asthma		40	62	Mrs. W.	Urticaria	53	0	0
Mrs. D.	Asthma	39	45	50	Miss C.	Hay fever	−10	0	20

Routine blood counts were made on this series of patients, and the only observation which we can make on these is that there is a tendency for the leucocyte count to be increased beyond normal. In practically all the cases studied there was an increase in the eosinophiles. Eosino-

philia due to such causes as intestinal parasites had been ruled out by previous stool examination.

We are studying also in this group of cases the skin reactions following the testing with a stool filtrate. The stool is emulsified in normal salt solution, allowed to stand for twenty-four hours in the ice box, is then filtered and cultured for sterility. This filtrate is then used for skin testing. We are attempting, by this method, to determine whether or not the bacteria and their products, as found in the stool, are different from the vaccines that we are making up from the cultures. A further report on this last subject will be made at a subsequent date.

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(For discussion, see page 612.)

ASTHMA OF LUETIC ORIGIN*

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THE association of bronchial asthma with syphilis has been recorded by numerous investigators. Some of them, however, are very emphatic in their assertions that the two diseases rarely coexist.

Ramirez[1] examined the records of 1000 patients diagnosed bronchial asthma and found that in 78 of them a positive Wassermann reaction was obtained. He summarizes the results of his study in the following: "1. That syphilis is not notably prevalent in asthmatics. 2. A clinical diagnosis of syphilis was not made in any of the patients. 3. Syphilis is not an etiologic factor in true asthma. 4. Antiluetic treatment does not influence asthma in cases where both coexist."

According to Duke[2] "patients with allergy have a relative immunity to chronic infections such as syphilis and tuberculosis, and that in them the disease runs a remarkably favorable course."

Hecht[3] reviewed the records of the asthmatic patients in the Cook County Hospital for the last four years and found among them a very small percentage of positive Wassermann reactions. He reports five patients with a history of a chancre with negative Wassermann reaction. His explanation of the above phenomena is rather interesting. He believes that nonspecific factors play a very important part in the so-called "specific" chemotherapy of syphilis. In fact, he feels that the merit of the "specific" chemotherapeutic agents rests in their nonspecific effect on the tissues which in turn react on the virus. He then proceeds to explain the mechanism of nonspecific therapy in chronic diseases: "It is because of the fact that the nonspecific agent 'shakes up' the normal individual and where he was stable before now makes him unstable and reactive thus causing the tissues to react to the virus with which he is afflicted. The asthmatic, on the other hand, because of frequent attacks produced by some antigenic substance, is already 'wound up,' and therefore it is understandable how such an individual may dispose of a luetic infection."

Zebrius[4] states that tuberculosis alone may induce a clinical picture closely resembling asthma and even actual asthma but that syphilis does not. Joltrain's[5] series of 252 cases yielded 24 positive Wassermann reactions. Lesne[6] reported 112 cases of asthma in infants of whom 12 had manifestations of hereditary syphilis. Both of them are of the

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opinion that it is unlikely that syphilis is a cause of asthma. Dufour[7] reports a number of patients in whom asthma and syphilis coexisted.

The purpose of this contribution is not to record the coincidence of the above two diseases but to call attention to the fact that syphilis may be an etiologic factor in the production of an asthmatic paroxysm. There have been no reports of such cases in the American literature except a casual remark by Rackemann[8] that "we have seen one or two cases in which treatment with arsphenamine did result in marked improvement."

Of the few cases reported in the French literature some are not authentic and others do not carry conviction. A very striking case is that reported by Pasteur-Vallery-Radot[9] who, while treating hundreds of cases of asthma had seen only one case of certain syphilitic origin. This was in a man forty-nine years old in whom various treatments for asthma brought no relief. Signs of aortitis led to suspicion of syphilis. The Wassermann test proved positive. After specific treatment was established the asthma disappeared.

Another case is that reported by Sezary and Alibert.[10] Their patient was a man fifty-one years of age who had continuous attacks of asthma for five years. Various treatments including climatic changes, failed to give any relief. After the first injection of sulpharsphenamine there was marked improvement which continued with further treatment.

CASE REPORT

S. G., aged forty years, came under my care December 15, 1929, because of paroxysmal attacks of dyspnea associated with cough and scanty frothy expectoration, fever, pain in the right chest, loss of weight and strength, anorexia, and epigastric distress aggravated by any food, of ten months' duration, although his gastric symptoms were of three years' duration. The attacks were preceded by an acute upper respiratory infection, were progressive in character, worse at night and on slightest exertion, and were always relieved by adrenalin. He owned and managed a laundry. He would invariably feel worse while visiting that place. There were no seasonal aggravations; no animal contact. He slept on feather pillows, cotton mattresses, and used woolen blankets. He had no other manifestations of allergy; no nasal surgery, and denied venereal diseases. One brother, whom I had the privilege to study, suffers from vasomotor rhinitis of the sensitization type and also has a positive Wassermann. Six months ago the patient was hospitalized in one of our leading hospitals where a diagnosis of active pulmonary tuberculosis was made, based on the clinical course of the disease and radiographic findings of a lesion in the right upper lobe. No positive sputa were obtained. Bronchoscopic examination was negative. He was advised to go to a sanitarium, which he did. For a while he noted improvement but shortly after he began to lose ground again. When I first saw him he had the typical appearance of an advanced case of pulmonary tuberculosis. He was orthopneic, cyanotic, markedly undernourished, asthenic, so much so that to answer a question was too much of an effort. Right pupil was irregular and smaller than the left. There was marked evidence of a subacute upper respiratory infection. Aside from marked fibrosis of right upper lobe the remainder of the chest was emphysematous and filled with many sibilant and sonorous râles, and expiration was markedly prolonged. The heart was of the

ptotic type, and aside from tachycardia it was normal. Tenderness was elicited in the right hypochondrium. The liver was palpably enlarged. Patellar reflexes were absent. No other neurologic abnormality could be obtained. He was admitted to the Mount Sinai Hospital for study on December 27, 1929. Temperature on admission was 100° F., pulse 120 and respirations 30. The blood pressure was 100/75. The weight 93 pounds.

Urine was negative. Hemoglobin and red blood cells were normal. White blood cells were 23,000 with 75 per cent polys. Five sputa examinations—one by the antiformin method—were negative for tubercle bacilli, spirilla, yeast, etc. Blood Wassermann yielded a mild positive on two occasions to Kahn and Kolmer technics. Lumbar puncture yielded a clear fluid under increased pressure, cytology and colloidal gold tests were not done, Wassermann was four-plus.

Examination by a rhinologist revealed thick pus in both nasal chambers and evidence of a pansinusitis. Antral puncture was negative. Local treatment preparatory to nasal surgery was advised.

Skin tests could not be resorted to because of the frequent use of epinephrin. However, skin tests were later carried out and moderate reactions were obtained to: house rust, orris root, pyrethrum, horse epithelium, also spinach, coffee, celery, tomato, lemon. The tests were made by the intradermal method, and the extracts were obtained from the Department of Applied Immunology, New York Hospital.

In spite of nasal treatments, dietetic management and medications, the attacks persisted requiring adrenalin very frequently and at times pantopon.

When the result of the Wassermann tests was imparted to the patient he admitted that a positive Wassermann had been obtained in a certain clinic about two years before, and two injections of neosalvarsan were administered. He was immediately placed on the following régime: 0.3 gm. of neosalvarsan intravenously and 0.1 gm. of bismuth intramuscularly alternating every fourth day. Iodides were also given but because of the presence of crackling râles in the right subclavicular region they were discontinued temporarily after the first two days, although later administered in larger dosages with perfect tolerance.

Within a few days his condition showed marked improvement; his attacks subsided, although cough persisted for some time; his appetite improved. After the completion of the first series of treatment of 12 doses of neosalvarsan and 12 of bismuth, he felt so good that he did not think further treatments necessary, although he was advised to the contrary. He gained 14 pounds between the first week of January and the second week of February, 1930. Within four weeks his symptoms recurred; he began to lose weight in spite of continuing the same diet, and digestive disturbances were marked, chiefly epigastric distress and tympanites. He was studied at the same time by Dr. Joseph Banks, a gastroenterologist, who after complete gastrointestinal studies diagnosed spastic colitis with stasis. An autogenous house dust extract was also administered since discontinuance of the specific treatment.

About the second week in March, 1930, Bismarsen was instituted and immediately improvement followed. He continued these treatments under the care of Dr. C. Antenson, reporting to me from time to time for a "check-up," also for spinal fluid drainage and serologic studies. His blood Wassermann was negative after two courses of Bismarsen—10 injections to a course, and spinal Wassermann two-plus. He also had tabetic pains in his legs which disappeared after the above treatments. He was given two courses of Bismarsen between March and July, 1930, and enjoyed good health until October, 1930. Although he did not gain weight his strength was definitely better so that he even could attend to his laundry business. In October, 1930, his symptoms returned although in a much milder degree. Under specific treatment he again promptly manifested results.

The last I heard from him was a few weeks ago when he informed me that he

has had no specific treatment since about August, 1931; that he has lost no time because of illness and that he has not had an attack for months. Dr. Antenson, however, in reply to my inquiry, informed me that the serum Wassermann was reported two-plus in November, 1931; that he had one moderate attack of asthma about two months ago, and Bismarsen was again resorted to but because of severe headaches following each injection the treatments were temporarily discontinued.

As far as the upper respiratory infection is concerned he still has frequent colds, and gets relief from local nasal treatment. He has, as yet, had no nasal surgery.

DISCUSSION

It is very important to stress the difference between syphilis of the lung and asthma of syphilitic origin. To a certain extent they bear the same relationship to one another as sinusitis to asthma of sinus origin. Not every case of sinus disease has the clinical syndrome of bronchial asthma, nor does every case of asthma have sinus pathology. Syphilis and asthma, as stated, frequently coexist and usually are two distinct clinical entities. Treatment of one has seldom any favorable influence upon the other. In this, all investigators of the subject are unanimous. I have personally seen and treated patients with pulmonary lues who at no time had manifestations of bronchial asthma.

The physical signs in this case were those of pulmonary fibrosis, and the x-ray examination showed an infiltrative lesion of the right upper lobe. The physical signs at present still persist, although no x-ray picture of the chest has been recently taken. Furthermore, it is not necessary that the syphilitic lesion should reside in the pulmonary tissue. Dufour[7] states that he had known of one patient with asthma who at the same time suffered from tertiary lesion of the skin of both legs. Treatment with gray oil cleared up not only the gummata but also the bronchial asthma.

Syphilis of the lung is a comparatively rare occurrence. Although numerous cases have been reported, few were definitely proved to be syphilitic. Pathologically it manifests itself chiefly in two forms: (1) gummata, and (2) interstitial pneumonia, which consists chiefly of pulmonary sclerosis. Clinically both forms may manifest themselves in pulmonary obstruction; hence, wheezing, spasmodic cough, and dyspnea resembling asthma may occur, but as Chevalier Jackson puts it, "not everything that wheezes is asthma."

The obstruction group in addition to the above, includes persistent thymus, substernal thyroid, aneurysm of the arch of the aorta, neoplasm of the lung and mediastinum, foreign body of the tracheobronchial tree or purulent tracheobronchitis. When respiratory embarrassment, such as wheezing, dyspnea and cough, occurs in the above, it should not be diagnosed as true asthma. True bronchial asthma, in the light of our present knowledge, is considered as an expression of hypersensitiveness to some antigenic substance depending upon many factors some of which are still inexplainable.

The mechanism which initiates the attack in cases of asthma of luetic origin is not definite. Milian believes that there is a syphilitic lesion of the vagus and that functional disturbance may be released by a variety of causes. Pasteur-Vallery-Radot[9] claims that the mechanism consists of a pulmonary irritative focus and a vagosympathetic dysequilibrium. Walker,[11] Rackemann[12] and others have proved the existence of bacterial allergy which means that the human being is sensitized to bacterial products which are probably mostly toxins.

The case presented by me is to be rightfully classified under bacterial allergy. The syphilitic infection in this case, as far as the positive Wassermann reaction is concerned, antedates three years the onset of the asthmatic paroxysms. The gastrointestinal symptoms which are of three years' duration are probably constitutional manifestations of visceral lues, either stomach or liver.

If we accept the theory of bacterial allergy as a hypersensitiveness to bacterial products, we can see how the products of *Treponema pallidum* may likewise produce similar reactions.

It is rather interesting that two brothers, presenting two different clinical manifestations of allergy, should be afflicted with lues. This familial element may be an expression of an atopic factor. Add to this the typical attacks and their invariable relief by adrenalin and the picture of true asthma is complete. Unfortunately I did not have the opportunity to observe the effects of specific chemotherapy on the vasomotor rhinitis.

As to the sinus pathology, even though surgery was urged by the rhinologists and in spite of frequent recurrent colds, it was not sufficient to excite an asthmatic paroxysm when adequate specific treatment was given.

In regard to frequency of positive Wassermann reactions in allergy, I feel that the statistical figures quoted would tend to show that they are not less frequent than positive serology among nonallergic individuals.

While it is well known that bronchial asthma, like many other chronic diseases has periods of remission, yet the episodes as cited seem too definite to be considered casual or coincidental. Failure to show improvement while removed from his place of business; elimination diets; local nasal treatments and administration of house dust extracts and vaccines; the sudden improvement upon the institution of specific treatment; the return of symptoms after inadequate chemotherapy and the marvelous improvement upon its readministration are facts which speak for themselves.

The fact that the Wassermann reaction is still two-plus and that there is a tendency to return of asthmatic paroxysms indicates clearly that the chemotherapeutic treatment has not been adequately administered.

SUMMARY

1. A case of true bronchial asthma of luetic origin is presented.

2. This form of asthma should not be confused with syphilis of the lung with which it may or may not be associated.

3. Asthmatoid symptoms, due to syphilis of the lung, belong to the obstructive groups and should not be classified under true asthma.

4. A suggestion is made that this case rightfully belongs under the classification of bacterial allergy and is probably due to hypersensitiveness to the toxic products of the *Treponema pallidum*.

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Society Proceedings

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

EIGHTH ANNUAL MEETING, ATLANTIC CITY, N. J., APRIL 30, 1932

(CONTINUED)

The Comparative Value of the Scratch and Intradermal Methods of Skin Testing in the Asthma and Hay Fever of Children. E. S. O'KEEFE AND L. B. BURGIN, BOSTON, MASS. (Abstract.)

Ninety-three cases of children under twelve years of age composed the series. Twenty-two cases had hay fever and seventy-one had asthma. The test substances were limited to a small group of pollens commonly causative of allergic symptoms.

The scratch tests were performed in the forearm using a 1:100 solution of the antigen prepared according to Coca's method. The intradermal tests were performed on the outer aspect of the upper arm using 0.02 c.c. of 1:1000 solution of the antigens.

The scratch test was positive in 45 per cent of the cases of asthma. The intradermal test was positive in 88 per cent of the cases of asthma.

The scratch test in the hay fever group was positive in 90 per cent of the series; the intradermal test was positive in 100 per cent of the hay fever patients.

The authors concluded that in the hay fever of children the intradermal test is only slightly superior to the scratch test. In the asthma of children, however, the intradermal test is much superior to the scratch test, and should be used in all cases where the scratch test has proved to be negative.

DISCUSSION

DR. SELIAN HEBALD, NEW YORK CITY.—I think again the question of concentration comes up. Using a 1:100 dilution for the scratch test is equivalent to 0.1 mg. nitrogen per c.c. for ragweed. In timothy it is also about 0.1 mg. per c.c. Using 1:1000 for the intradermal test, which is equivalent to 0.01 mg. nitrogen per c.c. it is surprising that Dr. O'Keefe did not get some constitutional reactions in his children.

The fact that Dr. O'Keefe got 90 per cent reactions with the intradermal tests of 1:1000 dilution, simply proves that these patients were very sensitive and the reason he did not get so large a figure in the asthmatic group is that they probably were less sensitive.

DR. COCA.—I should like to support Dr. Hebald's contention, recalling at the same time the studies of Dr. Fineman which so far as I can see ought to be applied to all results of skin tests, whether in asthma or hay fever, simply a question of concentration of the excitant in the material used for the test.

DR. W. T. VAUGHAN, RICHMOND, VA.—I should like to ask Dr. O'Keefe whether he relied on one negative scratch reaction to call it negative. That is one disadvantage of the scratch method. You do not know how much you are actually apply-

ing. I have seen individuals in whom I have felt sure, because of the date of the onset of the symptoms that the reaction should be positive. Sometimes they gave negative scratch reactions, but when I did a repeat, on another part of the body, I obtained a positive reaction, and this within no more than thirty minutes after the first test.

DR. E. S. O'KEEFE.—Regarding the concentration of the material used for the scratch test, it was sufficient to give 90 per cent reactions in hay fever; and there is no reason to believe, if the concentration was a factor in the case of great importance, that it would not have failed there as it failed in asthma in a certain number of cases.

In regard to the number of scratch tests we did, as a rule, one for each of the pollens. In that way we had some check on variations.

In the matter of constitutional reaction, I have not had any constitutional reactions in the intradermal tests in any of the children at any time. I think children are less subject to constitutional reaction than are adults.

DR. A. H. FINEMAN.—Of the 100 children with asthma and hay fever that Dr. O'Keefe mentioned in the paper, who were tested with comparative methods, serial dilutions were not employed with the scratch method. Pure pollen was dropped on the forearm and tests were made. In that series, we found in children under thirteen years of age positive reactions were obtained in a large percentage with the scratch method and practically the same with the intradermal method. We should bear in mind in testing children that it might be good policy to use pure powdered pollen with the scratch method first and if positive reactions are not obtained, the intradermal method should be employed.

In the previous comparative study serial dilutions were employed to determine the degree of skin sensitivity and that is where the distinction comes in.

Pollen Oil Dermatitis. A. BROWN, NEW YORK CITY. (Abstract.)

In a paper written in conjunction with Dr. E. L. Milford and Dr. A. F. Coca, it had been thought that the dermatitis caused by pollen and experimentally reproducible by cutaneous testing with pollen oil, is due to the presence in the oil of the atopic excitant. We have been able to show that the dermatitis is not due to the atopic excitant but to the oil itself. Hypersensitiveness to the pollen oil occurs in 15 per cent of hay fever subjects, in 15 per cent of atopic persons not subject to hay fever and in 15 per cent of nonatopic persons. It is thus to be classified as a contact dermatitis similar in its nature to dermatitis due to poison ivy, sumac and primrose.

The treatment of pollen oil dermatitis, naturally, must be with the oil rather than with the pollen. In two cases last year we were able to prevent all symptoms of dermatitis by injections of a one per cent solution of the pollen oil in three doses at two week intervals.

THE ASSOCIATION FOR THE STUDY OF ALLERGY

TENTH ANNUAL MEETING, NEW ORLEANS, LA., MAY 8 AND 9, 1932

The Use of Dextrose Intravenously in the Treatment of Bronchial Asthma. EDWARD MATZGER, SAN FRANCISCO, CALIF. (Abstract.)

In this preliminary report, hypertonic solutions of dextrose given intravenously are advocated for the relief of attacks of asthma when other

measures fail. Five hundred c.c. of a 20 per cent or 25 per cent solution or 1000 c.c. of a 10 per cent solution are found to be beneficial.

Various suggestions are made concerning the mechanism whenever dextrose is effective during an asthmatic paroxysm. The known fact that diabetes mellitus and asthma are rarely associated indicates that there may be an important relationship between an increased blood sugar and freedom from attacks. It is interesting that epinephrin which relieves asthmatic paroxysms likewise raises the blood sugar.

Another suggestion is that with the use of a hypertonic solution intravenously there is a definite flow of edema fluid from the tissues to the blood stream. Conceivably the edema of the bronchial mucosa may in that way be lessened.

Recent experimental work has indicated that dextrose given intravenously stimulates the reticuloendothelial system to greater activity, and since this system presumably participates in inducing immunity, this action may be responsible for the relief of asthma.

No case histories are given pending a complete report.

DISCUSSION

DR. M. MURRAY PESHKIN, NEW YORK CITY.—I am interested to learn what Dr. Matzger meant when he referred to "various toxic products liberated in the body." What was the age range of the patients receiving 500 c.c. of a 20 per cent solution of dextrose?

My experience from the standpoint of results in children to whom dextrose was orally administered in varying amounts along with or without spirits of ammonia, has been disappointing.

Dr. Matzger fails to state clearly the results of his experience, the dangers involved and the contraindications to his method of administering dextrose.

DR. HARRY L. HUBER, CHICAGO, ILL.—There was a statement made that diabetes and asthma very rarely went together. Last year in this meeting I reported two cases, one in a woman of seventy-five and another in a child of nine. There have been other reports.

There was another statement that the chief pathology of asthma is an edema of the mucosa. There are two main theories as to the cause of the dyspnea in asthma. One of them is the edema theory and another is the bronchial spasm theory, and each one of these has its supporters. There is a good deal of evidence to show that both of these work together in many of the cases. There are some cases where there is a great enough outpouring of mucus in the bronchi to cause the dyspnea, while in others, the bronchospasm is the essential feature.

The use of dextrose in asthma is emphasized in the reports of Oriel and Barber of England.

I have tried their method in some intractable asthmas and have not seen the marked benefit they describe.

DR. GEORGE PINESS, LOS ANGELES.—I want to reiterate what Dr. Huber said about diabetes, that we, too, have seen occasionally diabetics with bronchial asthma. It is not a common thing, but they do occur.

I should like to stress the fact that narcotics are contraindicated in the intractable asthmatics, as I have mentioned many times in meetings before this Society. Death actually occurring during attacks of asthma has always been associated with one or more doses of morphine, usually a second dose.

The object of giving dextrose, as I understand Dr. Matzger, is not to cure the

individual's asthma, but merely to support the individual, giving him fluids as well as food, and I believe under the circumstances it is indicated. It is a helpful measure and never harmful, and many of these patients, as a result of the increase of fluid, will begin to expectorate and come out of their attacks.

I do not believe that the object of giving the dextrose, from Dr. Matzger's standpoint, is that it may act as a curative or take the place of other medications such as adrenalin, but unfortunately these individuals, when you have to give them dextrose intravenously, have reached that stage where adrenalin does no good nor does caffein I think, whether it be dextrose or normal saline, it is a supportive measure that is worthy of use.

DR. MATZGER.—It may be interesting to know that unpublished work at the Hooper Foundation, under the direction of Carl Meyer, shows that he has been successful in preventing shock doses from killing experimental animals, by the use of dextrose between the first and second doses of the shock material.

In regard to the age groups, I have used it in the adult groups only. I have had no experience using it in children. He brought up the question of the use of dextrose in pneumonia. Dr. McLaughlin of Pittsburgh who had advocated this treatment has written me that he has discontinued using dextrose as a treatment for pneumonia.

The inferences that were not clear from my paper were probably made clear from Dr. Piness's discussion which emphasized the fact that rather than use narcotics, this is a physiologic and supportive measure which, if given with any degree of intelligence, will never lead to a dangerous reaction.

The question of edema in the underlying pathology of human hypersensitiveness is still an open one, in spite of the work that Dr. Huber did so beautifully with Dr. Kessler. We all agree that one lesion of asthma, at least, is edema of the bronchial mucous membrane.

Dr. Piness's discussion with regard to diabetes I welcome. I should like to get more evidence on hyperglycemia in severe bronchial asthma.

Whatever can be said against this use of dextrose I think can be answered by the objections to the general use of intravenous therapy. If proper care is used in the technic and in getting U. S. P. dextrose, there will be no danger of reactions.

I carefully avoided the term "glucose" throughout, because very often, if glucose is ordered, the druggist will sell old caramelized glucose, and this would definitely lead to a severe reaction. If dextrose is ordered, that takes with it the idea of a U. S. P. product, and there will be no danger of reactions.

Histological Changes in Allergic and Other Wheals. B. S. KLINE, MILTON B. COHEN, AND J. A. RUDOLPH, CLEVELAND, OHIO. (For original article, see page 531.)

DISCUSSION

DR. HARRY S. BERNTON, WASHINGTON, D. C.—What method was employed in rendering the skin anesthetic before removing a portion for histologic study?

DR. ALBERT H. W. CAULFIELD, TORONTO.—I should like to congratulate Dr. Cohen and his associates on this work. Would it be possible to add similar studies on tuberculin reaction?

DR. ROBERT W. LAMSON, LOS ANGELES.—I have been interested in the field of skin testing for a long time, hoping that some one criterion might be found to indicate whether or not an individual is allergic. You know that human dandruff sensitivity was supposed to be inclusive of the allergic but exclusive of all other patients. This test has not proved satisfactory.

At first it was claimed that a skin test with histamine would serve as this criterion. I have done some work on the histamine wheal, by the intracutaneous method, and have found no greater variations in the allergic than in the nonallergic person. There

were, of course, differences between individuals. One may characteristically give large wheals—whether an allergic or not; another, equally sensitive clinically, may give a small reaction. Those of you who do not hold that a patient's clinical sensitivity can be titrated by the size of the wheal, know that these differences in sensitivity are frequently found to pollen or to other allergens! The "tissue-paper" or "senile" type of skin often gives as large reactions as are found in the elastic skin of a younger individual.

Are the variations in histologic appearance related to age or physique of the patient or to the type of his skin?

DR. HARRY L. ALEXANDER, ST. LOUIS, MO.—This is a very fundamental piece of work, apparently something we have been waiting for for years. One question comes up which this may answer, and I think it does answer it, and that is where the eosinophiles come from. Many years ago it was thought they came from bone marrow, and there was a good deal of evidence to that effect. From these slides it appears that in the early stages the eosinophiles are in the blood vessels and then within the tissues. I should like to ask if that is correct.

Another surprising thing is that there should be a high eosinophilia in the histamine wheals. As I understand it, the two wheals were laid down side by side, one allergic and one histamine, and yet the eosinophiles appear as numerous in one as in the other. I wonder if a histamine wheal laid down in an allergic skin without an allergen wheal next to it would show the same thing. In other words, the histamine wheal was placed close to the allergen wheal and consequently the eosinophiles in the histamine wheal may have been induced by the contiguous wheal and not by histamine itself. I should like to inquire if this is not a distinct possibility.

DR. I. S. KAHN, SAN ANTONIO, TEXAS.—Decided clinical information is revealed by the natural corollary of this histologic study, the routine eosinophilic examination of the cells of the nasal discharge. For more than a year I have made such smears routinely in my office in practically every case where discharge was present. Eosinophiles can be demonstrated sooner or later in every single allergic rhinitis case if sought for under proper conditions, though in a few instances many examinations will be required. Allergic rhinitis fails to show such eosinophilia temporarily in my experience under the following conditions: (1) during periods of extreme severity when there are few or no cells of any kind; (2) during periods of allergic quiescence; (3) at times during periods of acute intercurrent infection.

The material for examination can be best secured by having a patient use a small cellophane handkerchief as a substitute for his own, and only when there is a spontaneous desire to evacute the nasal secretions. Forcible commanded blowing efforts are valueless. In hypersensitive patients whose symptoms are limited to nocturnal or early morning hours with allergic quiescence during the morning or with allergic quiescence during the balance of the day, leading to considerable diagnostic questioning and frequent overlooking of the hypersensitive state, diagnostic eosinophilia can be detected by the use of the cellophane handkerchief in the home during periods of activity, as specimens so secured will remain for several hours available for examination.

Fifteen chronic sinusitis cases for controls showed no eosinophilia; several other intended sinusitis controls showing eosinophilia turned out ultimately to be allergic.

DR. M. MURRAY PESHKIN, NEW YORK CITY.—I should like to ask whether Dr. Kline and his coworkers have made histologic studies from a traumatic wheal produced by the intradermal injection of a large amount of a 1:50 solution of pollen extract in cases of pollen asthma negative to the skin test?

DR. W. W. DUKE, KANSAS CITY.—I should like to ask Dr. Cohen if the wheals with pseudopods which follow injections of such substances as morphine, heroin, or

codeine are different from wheals which follow intracutaneous inoculation with histamine. In the latter case, we practically never find pseudopods.

I have wondered if this was due to some difference in the injected material. One frequently finds after an intracutaneous inoculation with such material as codeine, morphine, or heroin that a wheal will sometimes appear one or two centimeters away from the injected material, suggesting possibly a greater diffusibility of drugs of the morphine group as compared with histamine.

DR. RICHARD A. KERN.—I should like to follow up the idea that Dr. Alexander brought up as to whence the eosinophiles arise. There has been so-called evidence adduced by some to show that the eosinophiles develop in situ, on the basis of the conformation of the cells seen, some being cells with typical, lobed nuclei; others mononuclear and apparently entirely different cells histologically excepting as to the content of the eosinophilic granules.

Personally I have not been able to convince myself that these might not have been artefacts. I wonder if with the huge number of eosinophiles it was possible to determine whether the cells were characteristic eosinophiles as seen in the circulating blood, or whether there were differences.

DR. B. S. KLINE.—A few of the questions that have been asked I think Dr. Cohen should answer, and there are a few that I have not been able to get clearly in mind.

One question related to the reaction in a tuberculin hypersensitive individual. Dr. Goldblatt, in Cleveland, has been making histologic studies along that line and will report. I should have referred to the fundamental histologic studies of Arthus, Rössle, Gerlach, and others, in anaphylactized animals. The findings in human allergy are not unlike the changes observed early in anaphylactized animals by Rössle. In the studies in animals there have been discrepancies in reports, some claiming that the eosinophiles predominate for a long time and others that after a number of hours the polymorphneutrophiles are in the ascendency.

I think Dr. Cohen should discuss the anesthesia, the method of obtaining the specimens and also the nature of the skin, that Dr. Lamson asked about.

As far as gross appearance is concerned, when the specimens reached the laboratory, we saw no abnormalities of the epidermis itself. Furthermore, histologic examination showed no appreciable changes in this coat.

Concerning Dr. Alexander's question as to whether the eosinophiles arise in situ or come from the bone marrow, I agree absolutely with his observation of the slides. I think they show definitely that the eosinophiles come out of the blood vessels early.

I did not stress the fact that in the twenty-two-hour specimens the leucocytes are observed more extravascularly than intravascularly. At the twenty-two-hour stage there is very little exudation going on. The pictures suggest that the reaction is at its height perhaps at the six-hour period and begins to regress after that in the reversible reactions. These changes are much less severe than those associated with the Arthus phenomenon.

The interesting question of Dr. Kern I would not have mentioned. I am glad it was brought up, for it actually happens to be a fact that one can tell in the tissue preparations as easily as in films, the nature of the participating cells and that the majority of eosinophiles in and about the blood vessels have double nuclei. They are not polymorphous. I should say that I have a very strong impression, if not an actual conviction, that these eosinophiles do not arise in situ in the skin and that they are not altered polymorphneutrophilic leucocytes. Very few of them have polymorphous nuclei. They have one, two or rarely three little nuclear masses not connected by well defined chromatin filaments as is the case in segmented polymorphneutrophiles. To me they are definitely wandering eosinophile cells, and in the pictures, as Dr. Alexander observed, they look as though they come out of the vessels.

There has been an interesting controversy in the German literature about tissue eosinophilia, and the consensus of opinion, I think, is that the eosinophiles come from the bone marrow and these studies support that contention.

There was a question about the possible influence upon a histamine wheal of a regional allergen wheal in an allergic individual. I think it is fair to have a control of that sort, that is, to take some skin at a distance of about 5 cm. from the actual allergic wheal produced by an allergen in an allergic individual, to make absolutely certain that no changes occur at this distance. The histamine wheals in the allergic individuals in our series were started 5 cm. or more away from the allergen wheal; although it is conceivable that the allergen wheal may have had some influence on the histamine wheal, I question it. I think that the histamine wheal under these circumstances actually occurs as stated here; that it has no relation at all to the regional allergen wheal.

It is interesting to learn the general similarity of the nasal smears in allergic individuals to tissue changes observed in this series.

Concerning Dr. Duke's questions, we have written in the report that we hope to make a study of morphine, codeine, and other substances in allergic individuals to see whether these agents that produce hives in normal individuals will have a more marked tissue reaction in allergic individuals or not.

Dr. Cohen should answer concerning the pseudopods. The changes we observed have nothing to do with surface phenomena. Some of the most marked alterations in fact were observed in the subcutaneous fat.

I should have stated that in the specimen from individuals hypersensitive to cold, heat, and scratching, removed at thirty minutes (one was removed three hours after exposure), the reactions were very much like histamine reactions in nonallergic individuals. They were minimum reactions with nothing of the play of leucocytosis as in the allergic individuals.

DR. M. MURRAY PESHKIN, NEW YORK CITY.—Clinical experience has taught that there exists a certain group of patients with typical pollen asthma in whom the skin tests (scratch and intradermal technics) with concentrated pollen extracts, are negative. These patients are referred to as being skin refractory, and yet a large majority exhibit positive reactions with the dry pollen eye test. The intradermal injection of a large amount of concentrated pollen extract or any fluid for that matter, will produce a traumatic wheal. Has such a wheal been resected and subjected to histologic examination?

DR. B. S. KLINE.—I think we have a possible answer to your question in one of the seven allergic individuals. As I stated, in six allergic individuals at thirty minutes the reaction was moderate, considerable, or marked, and in one the reaction was slight. In that individual the eosinophilia was only 25 per cent. The general reaction was slight. It was not of a high degree, and it would lend some support to your contention that the individual might have given a more marked reaction if the material were applied to the ocular mucosa.

DR. MILTON B. COHEN.—With regard to the anesthesia, either before or after the wheals were made, depending on the time at which they were to be removed, usually thirty minutes before, the entire area is walled off with 1 per cent novocain.

As to the question of proximity of the wheals, we began them 5 or 6 cm. apart, and, if they came close together, we took the sections at the ends of the areas so that the portion where we took out the histamine would be 6, 7, or 8 cm. away from the corresponding ragweed wheal.

In addition all these sections were removed from areas where the swelling was produced by the reaction. We would make a small injection and take out the specimen from the periphery of the induced reaction.

There are many other studies and controls we want to make. We have not, Dr. Peshkin, tested exactly the type patient you are talking about.

Summer Dermatitis Due to a Common Weed. HARRY L. HUBER, CHICAGO, ILL. (For original article, see page 578.)

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—I want to bring out these points: first, that these cases reported describe the typical type of pollen dermatitis in that usually the exposed surfaces are affected.

Second, the question in my mind is: Is not there a possibility that some of the pollen may be on the leaf, the leaf being so broad and the pollen so fine; although we do know there are certain leaves which have a certain fuzz on them which will produce the irritating reaction, such as sumac and others.

The seeds presented in the pictures are of the female flower, and these seeds are probably the female flower, the pollen coming from the male flower on the same bush and head.

DR. RAY M. BALYEAT, OKLAHOMA CITY.—It has been our experience with people who have a dermatitis from pollen that if you test with the leaf you will get also a positive patch reaction. We believe that it is nothing more than the oil in the leaf, and the same oil in the pollen, that causes the reaction. It appears also that it is an oleoresin and not a volatile oil. For example, we have extracted the oleoresinous material and placed it on watch glasses so that it does not come in contact with the skin, and obtained no reaction. The same product on coming in contact with the skin will produce a positive patch reaction.

DR. HUBER.—The interesting thing is that these have been called pollen dermatitis cases. The thing that made me think it was not alone a pollen dermatitis was that the symptoms began so much before the pollen appeared in the air. It is a toxic material that is present long before pollen matures, and I think we are incorrect in calling it pollen dermatitis. There may be some cases where it is a true pollen dermatitis, but in many cases the lesions are also caused by other things. In those tests reported in literature, some gave immediate positive reactions and some only delayed reactions. It is hard to explain all of these variations if one assumes that the etiology is the same in all cases. If one allergist treats these cases successfully with a fat-free pollen extract, another has success with a pollen extract that has very little fat in it, and still another uses the pollen oil alone, either there is little specificity or they are treating different types of cases. I am going to treat my patients with an extract made from the leaves of the plants.

The Localization and Specificity of Cellular Sensitization. HERBERT J. RINKEL AND RAY M. BALYEAT, OKLAHOMA CITY, OKLA. (For original article, see page 567.)

DISCUSSION

DR. HARRY L. HUBER, CHICAGO.—This question of tissue fixation of antibodies and specificity is very interesting. I have one slide that I wish to show of a patient who is sensitive to all of the drugs that contain barbituric acid. Five years ago she had a chronic ulcer of the right eye and during that time had a swelling of the right eyelid. Following the treatment of this ulcer of the right eye, she learned that if she took any drug containing barbituric acid or its derivatives, she soon had a swelling of the right eyelid.

A few days ago she came to the hospital for observation for another condition, and one night the interne gave her one of the barbituric acid derivatives. I was asked to see her the next morning because of a swelling of the tissues about the right eye. This swelling persisted for two days. This is a good example of localized specificity.

DR. BALYEAT.—In preparing this subject for presentation Dr. Rinkel said to me, "We are not presenting a new subject. Dr. Alexander has presented the subject

under the topic of 'Skin Reactions.'" I said, "That is true, of course, but a subject that has fundamental principles ought to be discussed and rediscussed." Why? Because of the fact that the men in this country who are prominent in medical circles, other than the allergy men, do not recognize certain important facts that the doctor has presented. He presented one case, for instance, a young man, a doctor who lives in Oklahoma City, who developed attacks of dizziness similar to those Dr. Duke reported many years ago (Menière's syndrome), which represents a local manifestation of allergy. This young doctor had falling attacks. He would sit in the office and would become dizzy; he would develop a dull headache; vomiting would soon start, and unless he would lie down there would be a tendency for him to fall. He went to Philadelphia and to Boston and various other places and had different types of investigation from gastrointestinal to neurologic. He reported that after examination the doctor would say that there was no pathologic condition that could possibly cause such a chain of symptoms. In other words, he said he interpreted this statement to mean that he was a neurotic. An internist in our city sent him to us, and upon investigating his history we found that he had hay fever when he ate cantaloupe, his mother had migraine and his sister had hay fever. He gave a marked reaction to milk and a number of other foods. One food after another was extracted and additions were made, and we found by clinical trial that milk was the cause of his symptoms. In other words, when milk is taken entirely out of his diet he stays free from symptoms. When milk is added to the diet symptoms are produced.

These fundamental principles that doctor has discussed today are principles that many men of large clinical experience are not recognizing. They do not realize that specific sensitization may be localized.

DR. RINKEL.—I had hoped to have more discussion concerning the localization of sensitive cells in the skin. One of the reasons that I presented this paper was to stress the localization of sensitivity in the various types of dermatitis.

Dr. Huber's case just presented illustrates a typical case of contact dermatitis where sensitive cells are limited to the superficial epidermis. In one of our cases, severe systemic reaction occurred after testing with an ether soluble extract of *Helenium microcephalium*. This extract did not contain pollen. Intracutaneous and subcutaneous injections of the same material caused absolutely no symptoms.

The clinical importance of localization is greatest in cases of dermatitis. While the morphologic aspect of different cases of dermatitis may be identical, the immunologic mechanism responsible for symptoms may be atopic in one case and the result of contact in another. We err when we consider a case of dermatitis atopic because it improves on elimination of foods that gave cutaneous reactions.

We believe that when a patient comes in with eczema or dermatitis during the summer, plant life is to be considered before other factors. In these cases, the presence or absence of allergy in the family tree is of no significance. One other point, in scratch testing many of the delayed reactions are in reality contact reactions.

Perennial vs. Preseasonal Treatment of Hay Fever. LEON UNGER, CHICAGO, ILL. (For original article, see page 548.)

DISCUSSION

DR. W. W. DUKE, KANSAS CITY.—I have used the perennial method of treatment consistently now for three years and have consistently used the pollen solutions mixed with ephedrine and adrenalin and injected distal to a tourniquet. This slows down its rate of absorption. I no longer inject material near the skin but into the subcutaneous tissue. The tourniquet is left in place about five minutes so that the adrenalin and ephedrine will have time to constrict the neighboring vessels before the pollen is absorbed.

I have obtained results with this method of treatment which are quite different

from those obtained with the older preseasonal and coseasonal treatment. The skin tests have a greater inclination to become negative—in fact, in a large proportion of cases become so negative that you would hesitate to make a diagnosis of pollen sensitiveness based on skin tests. Very frequently skin tests with the material used in treatment give rise to no reaction whatever. It has led me to believe that the perennial method of treatment marks one of our greatest advances in pollen therapy. The use of adrenalin and ephedrine to hold the material local prevents reaction and makes it possible to use longer intervals than those mentioned by Dr. Unger without ill effect.

I am convinced from a three years' experience with the perennial treatment combined with the use of adrenalin, ephedrine, and the tourniquet that the dangerous reactions from pollen are caused by a too rapid rate of absorption of pollen rather than by overdosage or loss of immunity. If you inject pollen subcutaneously according to the general technic, you are sure sooner or later to inject some of the material into a lymphatic, capillary, venule, or artery and get a rate of delivery of the pollen into the patient's blood which is far beyond his tolerance. A reaction will then necessarily follow. I believe with the use of the tourniquet, as previously described, the pollen material would be held local by adrenalin and ephedrine even if it happened to be injected into a venule or artery and that the rate of delivery of the extract to the patient's blood would be slowed down to such an extent that a dangerous reaction would not ensue. During a period of three years giving perennial treatments at intervals of three to six weeks and even at intervals of two months, I have not had one reaction of importance.

DR. M. MURRAY PESHKIN, NEW YORK CITY.—In the last few years I have listened to several papers on the perennial treatment of hay fever and pollen asthma and in discussion, made the statement that the various authors omitted to mention whether or not they have selected a special group of patients for this form of pollen therapy.

Thus far I have gained the impression that the patients placed on perennial treatment were those who have done well on preseasonal treatment. My impression appears to be warranted since the incidence of constitutional (general) reactions is reported to be lower in those patients under the former plan of treatment.

A word of caution. The exact nature or chemical formula of a pollen extract is not definitely known. We do know that the injection of pollen extract in the human being does cause some response. It either stimulates, neutralizes something or creates new substances in the various organs of the body. Under the preseasonal plan of treatment the organism has at least a six months' respite from injections. During this rest period the body is afforded an opportunity to undo any damage that may have occurred. Under the perennial plan of treatment a patient is subjected to the injections of a foreign substance year in and year out. We are all familiar with the organic changes occurring in animals as a result of injections of a foreign protein over prolonged periods of time. How much harm the perennial treatment will do cannot possibly be determined in two years. Perhaps five years from now adverse reports may creep into the literature in the nature of neuritic or atrophic disturbances and even possibly myocarditis.

The perennial plan of treatment may prove to be less troublesome, more economical and more efficacious than the preseasonal plan. In spite of these attributes, along with the fact that this new plan of treatment holds a promise of cure from pollen asthma and hay fever, we should nevertheless caution that this form of treatment is merely in the stage of clinical experimentation and is to be applied by trained allergists only.

If I have given the impression that I do not employ the perennial treatment, I wish to state that is not correct. I merely wished to point out the possible dangers involved and also to curb its widespread use until such time when the treatment and its effects are better understood.

DR. MARION T. DAVIDSON, BIRMINGHAM, ALA.—I started perennial treatment on several cases soon after I saw Dr. Brown's first article, three or four years ago. I have about 8 or 10 cases now which are in their fourth season of perennial treatment.

I have given injections once a month. I have always given small amounts of adrenalin with the injections, and I have never had any reactions further than slight urticaria at the site of the injection, but never any constitutional reaction.

I have never made any attempt to select cases but have given the perennial treatment to all who would come for it.

DR. WARREN T. VAUGHAN, RICHMOND, VA.—In answer to the question that Dr. Peshkin raised concerning selection of cases, the only selectivity I make is that I put almost every one on who will go on. They select themselves. If anything, my cases are those that have not done so well because I try to sell them the idea of doing better on perennial when they have not done so well on preseasonal, but, in short, really there is no selection in my own work.

I hesitate to allow as long an interval as Dr. Duke. Ten days to two weeks is our usual interval.

DR. GEORGE PINESS, LOS ANGELES.—I want to say this about constitutional reactions: Constitutional reactions occur in the perennial cases because men insist on giving the maximum dosage after the season. It has been the custom with us where we have no choice but to give perennial treatment during the season, to drop back to a minimum dosage, which I call a desensitizing dose, to increase it before the onset of the season, to boost up to the maximum.

Another fact about reactions is that they depend on your ability to judge your patients' dosages. If you find a patient gets a reaction with a dose regardless of size, it behooves you to cut down the dose or repeat it instead of trying to increase it, and in that way minimize the chance of constitutional reactions.

Constitutional reactions just prolong the period of waiting for your reaction. If you are going to get a constitutional reaction by ordinary methods, you will get it immediately, and that is the time to get it, not after the patient has gone home and you are called upon to give emergency treatment.

The adrenalin temporarily prevents the reaction from coming on; but as soon as it wears off, then the reaction will occur anyway.

DR. UNGER.—The meetings we have annually give us an opportunity to express our differences of opinion, and if we all thought alike, there would be no reason for holding these meetings. I just happen to be one of those individuals who cannot see the idea of putting a tourniquet on a patient and giving adrenalin at the same time because I feel it is bad psychology.

I think that you immediately impress the patient with a fear of hay fever treatment. He wants to know why you put the tourniquet on, and you really make him afraid of pollen treatment. You certainly are not going to help the patient in that way. What you will do eventually will be to drive your practice away. If you regulate the dosage and you watch your patients, the number of reactions is very small. Many of the reactions I classified as constitutional were very mild. I counted anything a constitutional reaction in which some symptoms of hay fever or urticaria, or tightness in the chest occurred.

There were only 2 or 3 of those we had in the preseasonal groups which were severe, and all those were controlled promptly by adrenalin.

Again I wish to emphasize that I think once a month is too long an interval. I agree with Dr. Vaughan that two weeks is the proper interval. That gives 26 injections a year. It is not burdensome and works very well.

As far as Dr. Peshkin's remarks about the classification of cases, of course, all these are treated preseasonally first. You could not put them on any other treatment, and, of course, we think that the second year of treatment should give better results than the first year, but in our experience, repeating the second year of treat-

ment preseasonally does not always give better results by any means, and, furthermore, the reactions you got in a patient in 1929 treated preseasonally, you were as likely to get in 1930 and 1931 if you kept on treating preseasonally. If you work them up very gradually by the perennial method, at the end of two years or three years you will be able to get them up to a dose which I think will give a good clinical result.

DR. PESHKIN.—You have failed to answer my question. I asked what type of patient do you select for perennial treatment? I am well acquainted with the fact that perennial treatment is administered only to those patients who have previously undergone a course of preseasonal treatment.

DR. UNGER.—We do not select any particular patients. We should like every patient to go on it if he will, and especially the worst cases, the patients who do not give satisfactory results. If you put them on perennial treatment, you will get a much better result, I believe, than by continuing more preseasonal treatment.

As to the possibility that Dr. Peshkin points out, of giving some generalized damage to the body, as chronic myocarditis or hepatitis, we certainly have no proof that such a thing has ever occurred. We have electrocardiographic evidence of the fact that the heart is not damaged. Patients with asthma for years, many of them hay fever cases, who have had pollen hay fever or pollen asthma, seem to have no myocarditis, or no more than those without pollen treatment.

I see no reason why we should not urge general practitioners to give perennial treatment. I see several good reasons why people should go on perennial treatment. We had 3 reactions in perennial against 34 in preseasonal treatments. The perennial method lessens the reactions and, therefore, is the method of choice as far as I can see.

Dr. Piness said that the reactions occur because the men insist on giving the maximum dosage all year round. That is not true. We do not do that. If we get a patient up to 0.5 c.c. 1:100, we drop it to 0.1 c.c. and give that all year round. That is probably the reason why we get so few constitutional reactions, because our all-year-round injections are one-fifth, or one-tenth, or one-half of the dosage that we have given before. The patient has been able to tolerate double or triple or five times the dose and, therefore, can go ahead all year round and take the injections without trouble.

The application of the tourniquet should prevent the prompt reaction, which is the dangerous one, of which Dr. Duke has so often expressed himself. I do not believe the tourniquet will prevent those reactions which are delayed.

An Improved Coseasonal Therapy. WARREN T. VAUGHAN, RICHMOND, VA. (For original article, see page 542.)

DISCUSSION

DR. ALFRED M. GOLTMAN, MEMPHIS, TENN.—Dr. Vaughan's paper has been very interesting to me in that I have had similar experience with both the coseasonal and the perennial methods of treatment. For instance, during the tree hay fever season through which we are now passing in this section I divided my patients into three groups: first, those coming in with hay fever symptoms and treated coseasonally; second, those treated preseasonally; and third, those treated perennially. A comparison of results obtained in the three methods of treatment has revealed to me that those cases that are treated with small doses of the extracts of the specific pollens to which they are sensitive and those treated perennially do very much better than those that are treated only preseasonally.

In the coseasonal treatment and in those cases under perennial treatment that are extremely sensitive I use very small doses of extract, and in most of them, instead of giving them subcutaneously, I use an intradermal method. I usually start with 0.01 c.c. of that dilution of an extract which just fails to produce a skin

reaction by dermal testing. This is more or less a modification of Dr. Phillips' method of intradermal treatment. It differs from Dr. Phillips' method in that I do not try to produce a reaction as large as possible without inconveniencing the patient. I do not care to have large reactions, and I try to get by with as little reaction as possible as the doses are increased. As I said before I start with 0.01 c.c., say of a 1:5000 dilution. I increase this dose 0.01 c.c. daily up to 0.1 c.c. of this dilution. I continue to advance the dose up to the point of the patient's tolerance. Of course this varies in different patients, and I wish to say that to date I have not given a dilution over 1:500 in strength intradermally. The foregoing I consider a small dose method of treatment and a safe method which seems to obviate general reactions. Seeing these cases improve as they do with intradermal injections and minute doses, I think that the method should come into more general use and reports should be obtained from different sections of the country so that we all may see the actual effect of this method of treatment. The treatment of allergic patients varies not only with the individual but in different sections of the country. The higher doses reported as being given by some authorities absolutely could not be given with any degree of safety to my patients. To be specific it has been impossible for me to reach a maximum dose, say of ragweed pollen solution of 1:50 strength and one c.c. in amount. I have been able to get some cases as high as 0.25 c.c. of a 1:50 solution. However, most of my cases will get about 0.2 c.c. of a 1:50 dilution, and if I get this high I feel that I am doing well.

In building up ragweed hay fever cases to their maximum tolerance every now and then, say in about 10 per cent of cases treated, general reactions have been produced; and if these reactions occur near or at the onset of the ragweed season, a good many of these cases continue to suffer throughout the season. It is the consensus of opinion in those cases having general reactions that symptoms during the hay fever season are very mild or do not occur at all. In a good many of my cases having general reactions near the onset of the season the symptoms persisted, at least to frost, and in some for some time after.

MR. O. C. DURHAM, NORTH CHICAGO, ILL.—I should like to make one suggestion on Dr. Vaughan's paper. He said he did not understand why 5 units would produce antibodies effective in the coseasonal treatment. Remember that 5 units is the extract of 2500 granules of pollen and that the inhalation of 50 granules will produce symptoms. If 50 granules will produce symptoms, why should not 2500 produce enough antibodies to protect a patient? Only a few times in a season does a sensitive person inhale more than 2500 pollens in a day.

DR. HARRY L. HUBER, CHICAGO, ILL.—I should like to call your attention to two articles in recent numbers of the JOURNAL OF ALLERGY. One was on "Massive Doses in the Treatment of Pollen Disease," and the other was "Minute Doses in the Treatment of Pollen Disease," and the clinical results reported in these two were practically the same. In the summer of 1931, I arranged a suction apparatus that drew outside air through a menstruum that would hold pollens, and I was amazed at the small number of pollen grains found in that menstruum. This shows that the number of pollen grains actually inhaled is not very great and that those people who receive the tremendous doses of pollen extracts would have to breathe air floating full of pollen to get the equivalent amount of pollen allergen that is being put under their skin.

We all have seen patients terrifically sensitive to minute doses of pollen extract, and to some of them we can never give more than a tiny dose, but, strangely enough, they will go along and do as well or better than those who tolerate the maximum doses.

I agree with Dr. Vaughan that in many cases we do not need the maximum doses, and I feel sure that we are oftentimes overdosing our patients.

DR. VAUGHAN.—I should like to ask Dr. Goltman whether he was running it up to 1 c.c. coseasonally or preseasonally.

DR. GOLTMAN.—What do you mean?

DR. VAUGHAN.—I mean your cases that had an intractable asthma or hay fever that lasted through the season. Was it coseasonal or preseasonal?

DR. GOLTMAN.—Preseasonal.

DR. VAUGHAN.—You ran them preseasonally to a high dose and preseasonally they developed asthma or vasomotor rhinitis.

DR. GOLTMAN.—As I told you before these cases were treated preseasonally, and the injections of extract were given subcutaneously. As the maximum tolerance of the patients in question was reached just about the onset of the ragweed season, some developed general reactions. In some of them the symptoms persisted throughout the hay fever season; in some the symptoms were those of hay fever; in others asthma; and in two cases hay fever and asthma combined. Up to this time I was always of the opinion that in those cases getting general reactions as the maximum dose for that individual was approached that they would be relatively free from symptoms. From these cases I feel certain that this assumption does not always hold true.

DR. VAUGHAN.—That is rather surprising because I think the experience of most of us is that if you have a general reaction you are likely to be free from symptoms from then on.

The Management of the Dust Asthmatic. J. A. RUDOLPH AND MILTON B. COHEN, CLEVELAND, OHIO. (For original article, see page 574.)

DISCUSSION

DR. FRANCIS M. RACKEMANN, BOSTON, MASS.—I have two suggestions which might be helpful. First, my good experiences with a room at the hospital made relatively dust free with a rubber mattress and pillow and with filtered air, have suggested that it might be wise for me to purchase a rubber mattress and pillow. The expense was small and now I can loan my mattress and pillow to various patients for short periods of time to help them decide whether a new mattress will make a difference in their asthma or not.

Second, I find that silk floss mattresses are a very common source of trouble and more important than feathers.

DR. ALAN G. CAZORT, LITTLE ROCK, ARK.—I myself am very sensitive to house dust, and I notice that my house dust patients give the same history as I. It starts along in October with us, when we start closing the windows and turning on the heat. These cases are worse at night. I found that they are not sensitive and do not react usually to dust from rugs and things.

DR. C. ULYSSES MOORE, PORTLAND, ORE.—I wish to thank Drs. Rudolph and Cohen for the valuable ideas contained in their paper. It reminds me of a case which I believe will fit in well here and emphasize one of their points.

The patient was a former preacher who, when first seen by us, appeared to be seventy-five years of age. He complained of difficulty in breathing, especially at night. This was so severe that for five months he had been compelled to remain in a sitting posture and had done no work for three years. Every night for months he had taken from 12 to 20 hypos of adrenalin so as to live until morning. His own words were "I have suffered ten thousand deaths."

Some 300 scratch and intradermal tests were negative except for cotton seed which gave no wheal but only a lace-like erythema over an area about 3 cm. in diameter. As it was rather a questionable reaction he brought in dust from his room and his mattress. These gave no reaction at all. When asked what kind of a

mattress he was using he said, "Long fiber cotton. I raised the cotton and took it to the gin myself in Oklahoma." Further questioning brought out the fact that underneath this mattress was a cheap mattress of some kind. Dust from it gave a positive test.

Elimination of his cheap cotton mattress permitted him to get along on only 2 hypos of adrenalin the first night. The third night he slept in a recumbent posture. Treatment consisted in decreasing doses of ephedrine sulphate and an occasional adrenalin hypo. He improved so rapidly that he seemed to grow younger week by week. His actual age proved to be only fifty-three years. Within nine months he was working at a job at which he walked as much as 27 miles in a single day.

During this man's months in bed he had used as a nasal spray an oily solution of ephedrine without benefit, perhaps with harm. On the theory that the oil might be from cottonseed and hence contain some cottonseed protein it was eliminated at the same time as the mattress. I should like to know whether any one here has had trouble from the use of oils.

DR. MILTON B. COHEN, CLEVELAND.—I think I should like to say to Dr. Rackemann that instead of having to loan the man the rubber mattress, it is very convenient to tell your patient to get brown butcher's paper and put it around the mattress so it is all encased, and you can make a clinical test at any one's house and save expense until you have determined the necessity for dust precautions.

Certain Phases of Digestion in Relation to Allergy. E. L. MACQUIDDY, OMAHA, NEB. (For original article, see page 588.)

DISCUSSION

DR. FRANCIS M. RACKEMANN.—I believe this paper is quite important. I said yesterday that there was a fundamental background for all these cases of allergy and I am delighted to see this sort of approach to that problem. It is interesting to see how many of the laboratory procedures seem to show similar findings in the various allergic manifestations.

So far there is nothing very startling about these findings, but the approach, as I say, seems to me to be excellent.

DR. HARRY L. ALEXANDER, ST. LOUIS.—I should like to ask whether these values were taken during the attack or after the attack was over.

DR. C. ULYSSES MOORE.—I should like to ask (1) whether the P_H's of the urine were taken on the twenty-four-hour specimen, (2) whether any attempt was made to analyze the diets of these individuals from the standpoint of their acid, neutral, or basic ash, and (3) whether basic diets were used in treatment, and if so with what results.

DR. MACQUIDDY.—I thank Dr. Rackemann for receiving the message in the spirit in which it was intended. It is absolutely a preliminary report. We are not attempting to bring out anything new at this time.

In regard to Dr. Alexander's question, these urinary P_H's and stool P_H's were purposely run when the patients were not having allergic manifestations. They were taken from fresh specimens and repeated two or three times during the day to get an average P_H. We did not allow the urine to stand any length of time because of the changes which take place in urine.

In regard to the diet, in the experiment on the carbohydrate diet published recently showing a tendency for the stool to become acid, we have purposely refrained from putting them on any diet. All of the patients were on general diets. We are carrying on this work to see whether or not we can affect the findings that we have here.

Department of Reviews and Abstracts

Selected Abstracts

The Treatment of Chronic Colitis by Anaphylactic Shock and Blood Transfusion. Kalk, H.: Ztschr. f. klin. Med. **118**: 561, 1931.

The nonspecific treatment of chronic ulcerative colitis by various authors is discussed. Kalk in 1925 observed one case in which a colitis terminated immediately after an anaphylactic shock. Moreover, two similar cases came to his attention. Each had an intense colitis with fever, marked diarrhea, loss of weight and other attendant symptoms of the intractable form of the disease. Both were completely relieved after being subjected to severe anaphylactic shock. These cases led to a deliberate study of the subject.

Cases with severe colitis intractable to other measures were studied clinically and roentgenologically. Fever, persistent diarrhea, anemia and loss of weight were the principal symptoms. In 8 such cases anaphylactic shock was induced by the deliberate injection of horse serum. Twenty to 40 c.c. were injected intramuscularly, and after an interval of twelve to twenty days a second intramuscular injection of 20 c.c. was given. If no reaction occurred, 5 c.c. were given intravenously, and if this was not effective 8 c.c. to 10 c.c. were injected into the veins. In 5 cases shock was induced, and in 3 none occurred. In the latter large blood transfusions were given. In all these cases, either marked improvement or complete relief occurred.

Asthma From Food Odors. Feinberg, S. M., and Aries, P. L.: J. A. M. A. **98**: 2280, 1932.

The ingestion of various foods as a frequent specific cause of asthma is well known. It is not well known, however, that some of these foods give off volatile substances, especially during the process of cooking, that are capable of arousing attacks of asthma.

Three case reports are given wherein asthma followed the inhalation of steam coming from foods that were cooking. In the first case, cooking shrimps caused asthma. In the second, symptoms occurred on inhalation of steam from peas, beans, and lentils, and likewise in the third peas were the offender. The authors note that similar cases were observed in which the reaction consists of a rhinitis. They considered it advisable in treating individuals not to be entirely content

with the removal of foods from the diet, but to consider also food vapors.

Episcleritis Due to Allergy. Balyeat, R. M., and Rinkel, H. J.: J. A. M. A. **98**: 2054, 1932.

The authors report a case of definite episcleritis of ten or twelve years' standing. During this time the patient has suffered every five or six months with it. Symptoms were characterized by sudden onset of photophobia, lacrimation, and painful eyeballs. A number of ophthalmologists had been unable to ascribe any etiology to the condition. The patient gave a history of having had autumnal hay fever of twelve years' duration, and he was found positive to various pollens, particularly ragweed. At a later date he was found positive also to several other inhalant allergens and to ten foods. Institution of hay fever treatment and elimination of foods which gave a positive reaction resulted in complete relief of the episcleritis.

Propeptan Therapy in Urticaria and Allergic Diarrhea. Reiss, F.: Wien. klin. Wchnschr. **44**: 1598, 1931.

The author reviews the usual methods of treating chronic allergic urticaria, particularly the elimination diet. He stresses the disadvantages of this form of therapy and against it he contrasts the effectiveness of propeptan treatment. This consists of the administration by mouth before meals of peptone derived from the particular food under suspicion. Thus if a given number of foods known to be allergens are to be taken, peptone in tablet form from each of these foods is first taken. This apparently desensitizes the individual so that the hitherto offending allergen may then be tolerated. These propeptans are available commercially.

A case report is cited wherein chronic urticaria and diarrhea of long standing, after the ingestion of shell fish, were completely relieved when propeptan of each of the offending allergens (shrimp, prawn, and lobster) was taken three-quarters of an hour beforehand. In another patient with urticaria from pork, complete relief after pork propeptan was secured. Of interest is the fact that after a few weeks of such treatment the patient may lose his specific sensitivity and tolerate the food that formerly caused symptoms. It is likewise noteworthy that in cases where Witte's peptone was given and no results were obtained, propeptan was effective.

Severe Bronchial Asthma Apparently Due to Fungus Spores Found in Maple Bark. Towney, J. W., Sweany, H. C., and Hurar, W. H.: J. A. M. A. **99**: 453, 1922.

Ten employees of a railway tie plant, none of whom had had asthma previously, contracted severe pulmonary symptoms within the seven

months' duration of their employment. The earliest symptoms began within five months. The onset was acute, with cough and expectoration. This was followed very soon by shortness of breath, which eventually became the predominating symptom. Cough and dyspnea grew progressively worse as the men tried to continue at their work. In several cases there was a history of night sweats and substernal pain. In some there was a rise in temperature at the onset. Weight loss was general. Roentgen ray findings were typical in that there were mottled areas similar in many respects to those seen in pneumonokoniosis. These were soft, partially diffuse, from 3 mm. to 5 mm. in diameter, increasing in size and density toward the hilus. They were absent at the apex.

Of the 10 patients, 8 were bark peelers and the remaining 2 shoveled bark. Of some 200 other employees, there is no record of any case of asthma in men other than those whose work brought them in direct contact with bark dust. Seventy-five per cent of the wood used was maple. In most of the ties there was a black dust of the consistency of lamp black beneath the cork layer of the bark.

The plant shut down and the patients improved. There was a marked clearing of the x-ray shadows.

About this time similar cases began to occur at an automobile plant in the same locality. Similar conditions of handling wood were found. About 75 per cent of the logs were maple and these contained a dust quite like that appearing on the ties. Thirty-six men were affected. They were improved when away from the plant, and symptoms returned immediately after resuming work.

An examination of the dust taken from the maple logs showed it to consist of pure spores of a fungus. This has been tentatively identified as the conidial stage of a species of *Nummularia,* known as *Conoidosporium Corticola.* Positive skin reactions with spore extracts and macerated spores were obtained not only in the patients but in 5 controls working in the mill. Six controls living elsewhere gave negative reactions.

The spores injected subcutaneously into guinea pigs caused an inflammatory reaction. They are capable of causing a sensitization following parenteral administration in guinea pigs that resembles anaphylaxis in its pathologic aspects. The passive transfer of reagin was not demonstrated.

Histamine-Like Effects on Gastric Acidity Due to Cold. Horton, B. T., and Brown, G. E. Proc. Staff Meetings Mayo Clinic **7**: 367, 1932.

Horton and Brown, who had previously reported six cases in which local and general symptoms of hypersensitiveness to cold were exhibited, had occasion to observe nine additional cases since their report. The clinical syndrome was characterized by local and systemic

manifestations. The local effects on the skin were pallor during the period of exposure, with redness, swelling, and increased local heat on removal of the hands or exposed part from the cold environment. Following a latent period of from three to six minutes, a characteristic systemic reaction developed. This consisted of flushing of the face, a sharp fall in blood pressure, a rise in pulse rate, a tendency to syncope, and transitory recovery in from ten to fifteen minutes.

With the hands in cold water, and a tourniquet applied so as to cut off the venous return from the hands, no systemic reaction occurred until the tourniquet was released. Systemic reactions were then much more severe than if the tourniquet were not applied. These experiments suggest that a chemical substance of a histamine-like nature was produced in the skin following exposure to cold. The reaction produced by the release of this substance into the general circulation simulated exactly the effects of subcutaneous administration of 0.4 to 0.5 mg. of histamine.

The present work is an extension of previous experiments in that the effect of the release of skin substance on gastric acidity was observed. It was noted that a marked increase of gastric acidity was produced within a few minutes after the release of the tourniquet. Since this response of gastric acidity is identical to that obtained with subcutaneous injection of histamine, these experiments present still further evidence of the histamine-like substances elaborated in the skin of patients sensitive to cold when the skin is exposed to low temperatures.

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